CHIMP-B study

Statistical Analysis Plan

1 CONTENT

Administrative information

Trial and Trial registration	CHIMP: Effect of intranasal administration of palivizumab on experimental respiratory syncytial viral infection – a controlled human infection study EudraCT number 2020-004137-21
SAP version	1.0
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Based on study protocol version	2.2
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Version History

Version	Version date	Changes
1.0	12-dec-2023	n.a.

Signatures

Louis Bont, PI Date:	Daniela Cianci, statistician Date:

2 ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
ATS	American Thoracic Society
AUC	Area under the curve
CHIM	Controlled human infection model
CI	Confidence interval
DPI	Days post inoculation
EDC	Electronic data capture
ERS	European Respiratory Society
FDA	Food and drug administration
FEF25-75	Forced mid-expiratory flow
FEV1	Forced expiratory volume
FVC	Forced vital capacity
GLI	Global Lung Function Initiative
GLMM	Generalized Linear Mixed Model
IMP	Investigational medicinal product
IN	intranasal(ly)
LRTI	Lower respiratory tract infection
METC	Medical Ethical Review Board (Dutch: Medisch Ethisch Toetsingscommissie)
PCR	Polymerase chain reaction
PFU	Plaque forming units
RSV	Respiratory syncytial virus
RT-qPCR	Real-time quantitative PCR
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOB	Shortness of breath
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
TCID50	tissue culture half inhibitory dose
URTI	Upper respiratory tract infection

3 INTRODUCTION

3.1 SCOPE OF STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) for the CHIMP study (study B) was written in accordance with the International Conference on Harmonization topic E9 (Statistical principles for clinical trials, 1998), the CONSORT 2010 statement (Schultz et al, 2010), and the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials (Gable et al, 2017). The SAP was finalized and signed before database lock and deblinding.

3.2 STUDY OVERVIEW

Study B will be the controlled human infection model, in which 28 volunteers will participate and be randomly allocated to placebo or treatment groups. Study B will be used to show proof-of-concept of prevention of RSV infection through IN administration of palivizumab. The choice of a randomized controlled trial design will allow for minimization of the effect of individual patient characteristics through random allocation to treatment groups. The choice to inoculate a minimum of 1 hour after administration of study intervention is based on the minimal expected half-life of IN palivizumab of 4 hours. The half-life of IgG in the nasal epithelial lining fluid is not well established but due to mucociliary clearance it is expected that it is substantially shorter than in serum. Half-life of IgG in the nose of mice was determined to be 4 hours. The choice of 0.9% commercial nasal saline drops, which only differ from the intervention by the active ingredient, was based on commercial availability. Immunogenicity of the anti-RSV antibodies will be repeatedly measured by antidrug antibodies (ADA) in the serum and concentrations of palivizumab in the serum and nasal washes over a 14-day period to define pharmacokinetics. We collect nasal samples for pharmacokinetic data through 14 days after inoculation as it is twice the expected duration of protection (7 days) based on in vivo studies of IN palivizumab administration. Finally, only possible immediate toxicity is anticipated as we expect to have already observed long-term toxicity in extensive clinical use with intramuscular administration. Self-reported symptoms according to the FDA scorecard and SAE's will be used as the main safety outcome.

3.3 STUDY OBJECTIVES

3.3.1 Primary objective

The primary aim of this study is proof-of-concept of prevention of experimental RSV infection through IN administration of palivizumab as measured by reduction in AUC of viral load as determined by quantitative PCR from a daily nasal-wash sample from day 2 to day 14.

3.3.2 Secondary objectives

1. To define local and systemic safety of IN administration of palivizumab.
2. Measure pharmacokinetics and pharmacodynamics of palivizumab in serum and nasal washes.
3. To measure anti-drug antibodies (ADA's) to palivizumab.
4. To measure lung function over time pre and post inoculation (Peak Expiratory Flow, FEV1, FVC, and FEF25-75) [spirometry].
5. To characterize leukocytes pre- and post-inoculation [nasal scrape].
6. To determine cytokine and chemokine profile pre- and post-inoculation [nasosorption].

7. To measure microneutralization of RSV-antibodies pre and post inoculation [blood].
8. To measure symptom profile over time in study participants.

4 STUDY DESIGN

4.1 SAMPLE SIZE

Our sample size calculation is based on the following reasoning and assumptions. Our primary outcome measure is the amount of viral load measured repeatedly over time within an individual participant. The overall viral load will be summarized through the Area under the viral load curve (AUC). In each arm of the trial the distribution of AUCs will be a mixture due two different subpopulations: a proportion of participants in whom there will be no viral load (AUC=0) because the challenge did not lead to infection (expected proportion in the placebo group 45%) and in the prophylaxis group we of course expect again 45% plus an additional proportion in whom prophylaxis prevented infection. In the remaining participants in whom infection did occur (AUC≠0), we expect the AUC under the log transformed values to be normally distributed with a certain mean and a standard deviation (SD).

Because of this relatively large proportion of participants with an AUC=0, the distribution of the AUC in each arm will be extremely non-normal, and non-parametric testing needs to be performed to demonstrate a difference in distributions between the two arms using the Mann-Whitney test.

Our sample size calculation is based on the following assumptions:

Placebo group:

- 45% will have an AUC=0 (expected proportion in whom infection will not occur). This assumption is based on an expected 55-65% infection in the placebo arm based on two CHIM trials published in the New England Journal, n=65 (DeVincenzo, NEJM 2015) and n=137 (DeVincenzo, NEJM 2014) as well as personal communications with Chris Chiu and Peter Oppenshaw (Imperial College), two experts in RSV human challenge trials.
- In the remaining 55% the mean AUC under the log10 PFU x hr/ml will be around 500 with an SD of 200 (Devincenzo NEJM 2015)

Prophylaxis group:
It is expected that prophylaxis will lead to the following changes:

- the proportion of participants with an AUC=0 will increase from 45% to 90%. We expect abortive infection (effect size close to 100%) as palivizumab is expected to prevent viral replication in the upper airways. To ensure sufficient power, we used a more conservative estimate of the expected effect size, assuming that the proportion of patients without infection will increase from 45% in the control arm to 90% in the treatment arm.
- In the remaining 10% the mean AUC under the log10 PFU x hr/ml will be lowered to 200 with an SD of 75

To demonstrate a difference in distribution in AUC between these two arms using a Mann-Whitney test with a power of 80% and a two-sided alpha of 5% requires a total of 14 participants in each group. These numbers are based on simulations using 5000 Monte Carlo samples based on the mixture of distributions described above.

4.2 RANDOMIZATION AND BLINDING

Non-stratified block randomization was performed via the randomization tool of Castor electronic data capture (EDC) platform. Block sizes of 2 and 4 were used. It is a double-blind study: all protocol-associated investigators, research nurses, site monitors, data management and biostatisticians will be blinded to treatment assignment. The pharmacy knows which trial number is linked to which treatment intervention (palivizumab or placebo). The research investigators responsible for statistical analyses remain blinded until both the PCR data of nasal lavage days 2-14 and Castor database are locked, at which time the key will be linked back to the subject numbers.

5 OUTCOME MEASURES

5.1 PRIMARY OUTCOME PARAMETER

The primary endpoint is the area under the curve (AUC) of RSV viral load expressed as RSV copies/mL. Cycle threshold (Ct)-values obtained via the RT-qPCR assay from a daily nasal-wash sample from day 2 to day 14 (*Variable name "Viral_load_Ct_[participant number]_[DPI]"*) will be calculated into RSV copies/mL (*Variable name "Viral_load_copies_[participant number]_[study day]"*) using a calibration line (see 6.1 Data preparation).[1] The AUC is calculated as Log_{10} copies/mL over time (day 2-14) per study participant (*Variable name "Viral_load_AUC_[participant number]")* and the median AUC Log_{10} viral load is calculated for the treatment arm *(Variable name "Viral_load_AUC_median_palivizumab*") and placebo arm *(Variable name "Viral_load_AUC_median_placebo*") with interquartile range. The limit of detection of the PCR assay is Ct<45 which is equivalent to a viral load of 790 copies/mL.

Nasal lavage samples are retested on qPCR if:

- The internal control (IC) is outside the acceptance limits, in which case the individual sample is remeasured;
- The positive control is below the acceptance limits, in which case the entire plate is remeasured;
- The negative control is positive, in which case the entire plate is remeasured;
- The non-template is positive, in which case the PCR extraction of the entire plate is repeated;

Retesting will also occur if viral load is deemed possibly inaccurate during data cleaning, i.e. viral load over time does not show a convex curve.

The new test results replace the previous PCR data.

5.2 SECONDARY OUTCOME PARAMETERS

5.2.1 Symptom profile

Participants self-reported their symptoms on day 0-10, 14 and 25 in symptom diaries. For each symptom, a score of 0 (absent) to 3 (severe) was assigned. Both upper respiratory tract (URT) symptoms and lower respiratory tract (LRT) symptoms were recorded to calculate a URT and LRT symptom score per day.

[1] Alma van der Pol, J.Clin.Biol Oct 2010.

URT symptom score (*Variable name "Totaal_score_dagboek_algemene_klachten_Totaal_score_Dag xx*) is the amount of points (0-3 per symptom) cumulated for eight URT symptoms: sneezing, headache, general feeling of being sick, fever or chills, runny nose, nasal obstruction, sore throat, cough. Since 8 symptoms were scored per day, a total of 24 points could be obtained per day. LRT symptom score (*Variable name "Totaal_score_dagboek_lage_luchtweg_klachten_Totaal_score_Dag* xx) is the amount of points (0-3 per symptom) cumulated for five LRT symptoms: cough on waking, wheeze on waking, daytime cough, daytime shortness of breath (SOB), nocturnal cough/wheeze/SOB. Since 5 symptoms were scored per day, a total of 15 points could be obtained per day.

5.2.2 Anti-RSV antibodies

Anti-RSV-PreF antibodies will be measured in mucosal (nasal and/or oral) and serum samples pre- and post-inoculation. Anti-RSV-PreF IgG and IgA are measured using enzyme-linked immunosorbent assay (ELISA) and expressed as ng/mL or µg/mL as appropriate. Microneutralization assay will determine the neutralizing capacity of mucosal and/or serum samples expressed as the half inhibitory dilution (ID50).

5.2.3 Anti-drug antibodies (ADA's)

The measurement of any local or systemic anti-drug antibodies against palivizumab will be decided in a post-hoc setting. We measure ADA's because a humoral response to palivizumab can explain reduced efficacy and loss of therapeutic benefit if found in high concentrations. Immunogenicity incidence rates vary from 0-42% for recently approved mAbs [Clin Transl Sci 2018].

5.2.4 Lung function

Spirometry was performed on day 0-10, 14 and 25. The FEV1, FEV1 predicted, FVC, FVC predicted, FEV1/FVC-ratio and PEF were selected from three correctly performed maneuvers. Results were graded using the grading system recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS). Measurements with scores A to D (*Variable name "d*xx*_longfunctietest_kwaliteitsscore_GLI")* were included in the analyses. When the results had a poorer quality score (the difference in FEV1 of two measurements was >0.250 L), they were found not to be reproducible and therefore unreliable. The predicted values of FEV1 and FVC were calculated according to the Global Lung Function Initiative (GLI) standards. Change in FEV1 predicted (*Variable name "d*xx*_longfunctietest_FEV1pred")* over time was used to compare the lung function of the treatment arm to lung function of the placebo arm.

5.2.5 Infection parameters

The measurement of nasal pre- and post-inoculation cytokines and chemokines, as well as serum infection parameters will be decided in a post-hoc setting.

5.2.6 Viral titration

RSV infectious viral titer in nasal washes from days 0-25 is determined by half tissue culture infectious dose (TCID50) assay and expressed as RSV TCID50/mL (Variable name "*Viral_load_TCID50_[participant number]_[study day]*"). The AUC is calculated as Log_{10} TCID50/mL over time (day 2-14) per study participant (*Variable name "Viral_load_TCID50_[participant number])* and the median AUC Log_{10} viral load is calculated for the treatment arm (Variable name "*Viral_load_TCID50_median_palivizumab*") and placebo arm *(*Variable name *"Viral_load_*TCID50*_median_placebo*") with interquartile range. The limit of detection of the TCID50 assay is 3.16 TCID50/mL.

5.3 SAFETY PARAMETERS

A list of safety data on local and systemic (severe) adverse events will be collected as defined in the study protocol (C1. Onderzoeksprotocol NL78591.041.21 Versie 2.2 dd. 19-7-2023):

5.3.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product / the experimental infection. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

5.3.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

5.3.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorized medicinal product;
   - Investigator's Brochure for an unauthorized medicinal product.

The sponsor will report expedited the following SUSARs through the web portal ToetsingOnline to the METC.

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

6 STATISTICAL ANALYSIS – GENERAL REMARKS

6.1 DATA PREPARATION

Before statistical analysis, data sources will be merged using R software. Excel sheets containing the Ct-values and copies/mL of nasal washes will be merged with the data collected in Castor based on the following variables: “Visit name”, “External IDs#1#Name”, and “Study Day”.

The RT-qPCR assay will generate Ct-values of nasal lavage samples. A calibration line will be used to convert the RSV Ct-values into RSV copies/mL using a linear equation:

$$\frac{Copies}{ml} = 10^{(14.72909 - 0.26302 \cdot Ct)}$$

At a later phase, we will attempt to replace the current calibration line and corresponding equation obtained in 2009 with electron microscopy with a calibration line using a plasmid control for the N gene copy.

6.2 INTERIM ANALYSIS

Not applicable.

6.3 HANDLING OF MISSING DATA

Missing data will be handled differently depending on the type of data:

- **Symptom data** In case of missing symptom data, we will impute symptom scores of 0 (= no symptoms).
- **Lower limit of detection imputation** In case of measurements below the lower limit of detection, we will impute halfway between 0 and the limit of detection (LOD) of the appropriate assay as the missing data point. The LOD for viral load in PCR is 790 copies/mL.

We will not impute data in any other missing data cases.

6.4 HANDLING OF MULTIPLE TESTING

Multiplicity does not apply in testing the primary hypothesis since there is only one primary endpoint. However, in testing the secondary equivalence hypotheses, no correction for multiplicity will be made since the latter inferences are exploratory.

6.5 STATISTICAL COMPUTER SOFTWARE

Analyses will be performed in R (version 4.0.3 or higher), SAS Enterprise Guide (version 8.2) and/or SPSS (version 29.0.0.0).

6.6 TIMING OF ANALYSIS

The primary analysis and the secondary analyses on symptoms profile will be performed after the PCR measurements of nasal lavage at 14 days post inoculation (DPI) are performed and all follow-up data have been collected. At that time, the PCR database and the Castor database will be locked and the data will be unblinded.

6.7 SUBGROUP ANALYSIS

For subgroup analysis, the following subgroups will be distinguished:

- **Symptomatic versus asymptomatic participants.** Participants are symptomatic if two or more of the following are present:
    - A cumulative clinical symptom score of 14 or greater over a 6 day period.
        - Totaal_score_dagboek_algemene_klachten_Totaal score_Dag 2-14 ≥ 14
    - Nasal discharge is present on three or more days over the six-day period post viral inoculation.
        - pat_dagboek_algemene_klachten_Snotneus Answer option ≥1 for at least 3 different days (Day 2-14)
    - A subjective impression of a cold developing. This latter criterion is used because there are a few subjects who have had a very strong subjective impression of a clinical cold but the cumulative clinical score does not reach the arbitrary cut-off level
        - Subjectieve_klachten 1=Yes
- **RSV positive versus negative participants.** Participants are defined as RSV positive if the PCR is positive on 2 consecutive days after study day 2.

We will perform descriptive statistics using the above-mentioned subgroups for the primary analysis and secondary analysis on symptoms profile.

6.8 SUBJECT DATA SETS

All randomized subjects will be included in the analyses. Given the study characteristics, no other analysis populations will be defined.

6.9 SENSITIVITY ANALYSIS

Not applicable.

7 STATISTICAL ANALYSIS

7.1 DESCRIPTIVE STATISTICS

Summary statistics for continuous data for each timepoint (if applicable) per arm and total for the randomized groups will be presented as follows:

- numbers of non-missing observations & missing observations
- mean & standard deviation (SD) or Median, Q1 & Q3
- minimum & maximum

Summary statistics for ordinal and nominal data for each timepoint (if applicable) per arm and overall for the randomized groups will be presented as follow:

- number of non-missing and missing observations
- number and percentages of observations in each arm, where percentages will be calculated using the non-missing observations only.

The unit of the parameters will be always specified (if applicable). All listings will be sorted by participant number.

Data may be investigated by using visual tools (e.g., histogram, box-plot, scatter plot, forest plot) to aid the presentation of information.

7.2 ANALYSIS OF PRIMARY ENDPOINT

The primary endpoint is the AUC viral load expressed as copies/mL as measured by the RT-qPCR assay from viral load measurement from day 2 through day 14. This analysis will be performed to test the null hypothesis that there is no difference between the distributions of the AUC viral load in the palivizumab 1 mg/mL arm and placebo arm. The alternative hypothesis is that there is a difference in the distributions of the AUC viral load between treatment groups. The test will be two-sided, with the level of significance set at 0.05.

7.2.1 Statistical approach

Descriptive statistics for the primary endpoint will be presented as described in 7.1 Descriptive Statistics.7.1 In addition, the percentage of patients without viral load per group will be shown and a graph of the median (IQR) viral load over time per group (see 8.1 Appendix A: Mock tables and figures).

For the primary analysis, the AUC viral load will be calculated for each participant using the R function trapz (package caTools). The Mann-Whitney U Test will be used to compare the AUC distributions between the two groups.

7.3 SECONDARY ENDPOINTS

Quantitative assessments of symptom scores, lung function, and antibody titers and function will be summarized using descriptive statistics (see 7.1 Descriptive statistics).

7.3.1 Symptom scores

Descriptive statistics will be provided for each symptom, by timepoint, in total and per treatment group.

URT symptom score and LRT symptom score from day 2-14 will be analyzed with two Generalized Linear Mixed Model (GLMM). The models are described below:

- outcome variable: symptom score (one in each model)
- Fixed effects: treatment group, time of recording of the symptoms included as continuous variable, interaction between treatment group and time
- Random intercept.

Estimates of the scores with 95% CI per treatment group at each time point and differences between groups at each time point with 95% CI will be provided.

In the eventuality that the GLMM will not be able to produce these estimates (e.g., due to the small sample size), descriptive statistics will be produced by group and for differences between groups for each time point.

7.3.2 Anti-drug antibodies

The analysis of any local or systemic anti-drug antibodies against palivizumab will be decided in a post-hoc setting.

7.3.3 Lung function

We expect a decrease in FEV1 predicted in the infected group, which will be larger in the placebo arm and therefore an overall decreased lung function in the placebo group compared to the intervention group. To analyze lung function we will use a mixed effects repeated measures model (13 timepoints per participant). We will use a repeated measures analysis over time by treatment arm, with the baseline lung function as covariate. We will look at FEV1 percent predicted, FVC percent predicted and FEV1/FVC.

7.3.4 Antibody titers and function

The analysis of antibody titers and function will be decided in a post-hoc setting.

7.4 SAFETY ANALYSES

Summary statistics and listings of AEs and SAEs will be produced for the placebo and the intervention group. We will calculate the cumulative proportion of patients with local/systemic AEs (all severities combined) in both arms. We will not perform a baseline measurement. Using these proportions, we will calculate a risk difference with 95% CI.

7.5 CHANGES TO PROTOCOL-PLANNED ANALYSIS

In protocol version 2.2, several secondary objectives were listed. Before study start, it was decided that objective 5 “To characterize leukocytes pre- and post-inoculation [nasal scrape]” would no longer be pursued due to the invasive sampling method in combination with the lack of laboratory protocol for immediate sample processing. The nasal scrape was taken out of the sampling workflow and therefore objective 5 will not be included in the analysis.

Also, objectives 2 “Measure pharmacokinetics and pharmacodynamics of palivizumab in serum and nasal washes” and 6 “To determine cytokine and chemokine profile pre- and post-inoculation [nasosorption]” were decided not to include in the analysis.

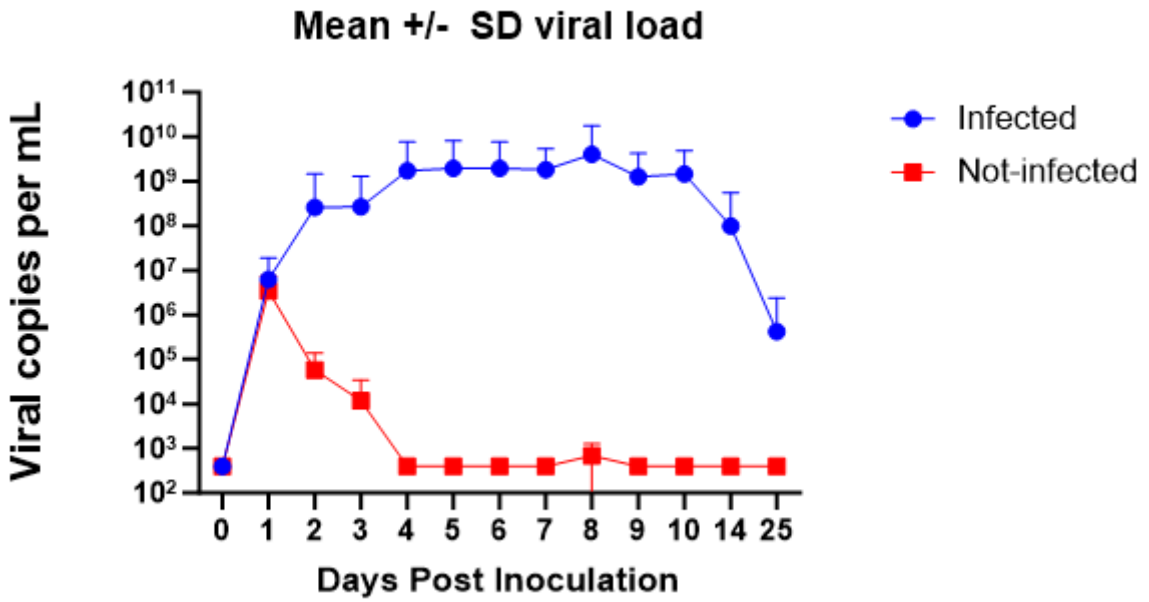
8 APPENDIX

8.1 APPENDIX A: MOCK TABLES AND FIGURES

Table 1 Baseline characteristics of study participants.

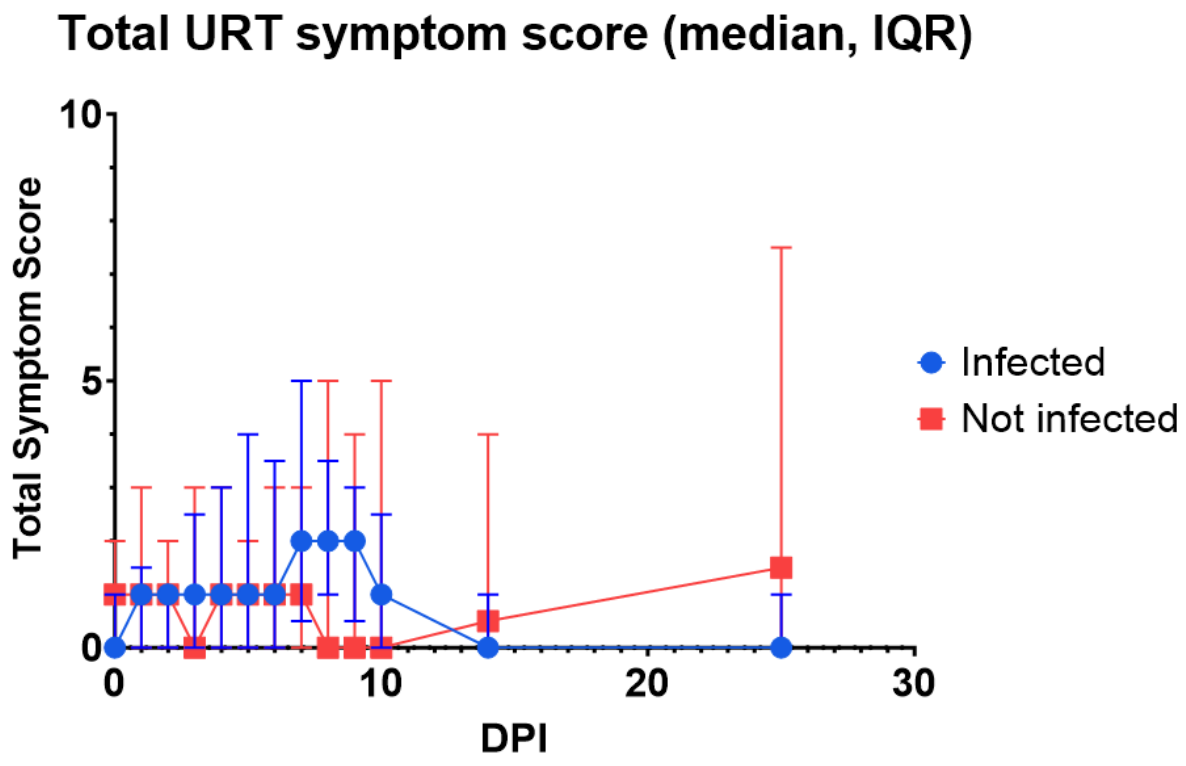
	Palivizumab (n = xx)	Placebo (n = xx)	Total (N = 28)
Female, n (%)			
Age, median (IQR)			
Education – postgraduate, n (%)			
Asthma			
No, n (%)			
In childhood, n (%)			
Eczema			
No, n (%)			
In childhood, n (%)			
Allergies			
None, n (%)			
Pollen, n (%)			
Specific plants, n (%)			
LRTI in the last year, n (%)			
Chronic illness, n (%)			
Smoking history			
Never, n (%)			
Past, n (%)			
Current, n (%)			
Baseline Lung Function			
FEV1 Predicted			
Mean, %			
Median, %			
Range, %			
FVC Predicted			
Mean, %			
Median, %			
Range, %			
FEV1/FVC			
Mean, %			
Median, %			
Range, %			

Figure 1 Viral load over time



Groups will be replaced with Palivizumab vs Placebo

Figure 2 Symptom scores over time



Groups will be replaced with Palivizumab vs Placebo

8.2 APPENDIX B: LIST OF VARIABLES

8.2.1 Baseline case report form

Variable	Answer option	Variable name Castor
Study ID	CHIMP-B-XX	
Date	DD-MM-YY	baseline_CRF_datum
Filled out by	[Name]	baseline_CRF_ingevuld_door
Informed Consent (IC)	Yes / No	baseline_CRF_toestem
IC version		
Inclusion criteria		
Age between 18 – 55 years	Yes / No	baseline_CRF_leeftijd
Exclusion criteria		
Children < 3 years old at home		baseline_CRF_kinderen_onder_3
People older than 65 years old at home	Yes / No	baseline_CRF_excl_65_jaar
Chronic of acute medical condition	Yes / No	baseline_CRF_excl_medische_aandoening
Chronic cold	Yes / No	baseline_CRF_excl_neusverkouden
Nasal obstruction	Yes / No	baseline_CRF_excl_neusobstructie
Use of nose spray/medication	Yes / No	baseline_CRF_excl_neusspray_medicatie
Nose surgery before or during study	Yes / No	baseline_CRF_excl_neusoperatie
Pregnancy	Yes / No	baseline_CRF_excl_zwangerschap

8.2.2 Baseline questionnaire

Variable	**Answer option**	**Variable name Castor**
Sex	Male / Female	baseline_CRF_geslacht
Age	[numerical]	baseline_CRF_leeftijd
Highest completed education	None / Primary school / VMBO / HAVO / VWO / MBO / HBO / University	baseline_CRF_niveau_opleiding
Asthma physician diagnosis	Yes / No	baseline_CRF_anam_astma
Eczema physician diagnosis	Yes / No	baseline_CRF_anam_eczeem
Allergic	Yes / No / unknown	baseline_CRF_anam_allergisch
Pollen	Yes / No	baseline_CRF_anam_allergisch_waarvoor#pollen/stuifmeel

Dust mite	Yes / No	baseline_CRF_anam_allergisch_waarvoor#huisstof/huismijt
Pets	Yes / No	baseline_CRF_anam_allergisch_waarvoor#bepaalde huisdieren
Medication	Yes / No	baseline_CRF_anam_allergisch_waarvoor#bepaalde medicijnen
Food	Yes / No	baseline_CRF_anam_allergisch_waarvoor#bepaald voedsel
Other	Yes / No	baseline_CRF_anam_allergisch_waarvoor#overig
Pets	[Free text]	baseline_CRF_anam_allergisch_huisdieren
Medication	[Free text]	baseline_CRF_anam_allergisch_medicijnen
Food	[Free text]	baseline_CRF_anam_allergisch_voedsel
ther	[Free text]	baseline_CRF_anam_allergisch_overig
>1 LRTI in past year	Yes / No	baseline_CRF_anam_lwi
Amount of LRTI in past year	[numerical]	baseline_CRF_anam_lwi_aantal
Use of medication	Yes / No	baseline_CRF_anam_medicijnen
Which medication	[Free text]	baseline_CRF_anam_medicijnen_welke
Medical condition	Yes / No	baseline_CRF_anam_med_probleem
Which condition	[Free text]	baseline_CRF_anam_med_probl_welk
Chronic illness	Yes / No	baseline_CRF_anam_chron_ziekte
Which chronic illness	[Free text]	baseline_CRF_anam_chron_ziekte_welke
Smoking	Yes / No	baseline_CRF_anam_roken
Duration of smoking	[Free text]	baseline_CRF_anam_roken_hoe_lang
How many cigarettes per day	[numerical]	baseline_CRF_anam_roken_hoeveel
Other remarks	[Free text]	baseline_CRF_anam_ov_opm

8.2.3 Study Diary

Variable (*X=0-10,14,25)	Answer option	Option Value
pat_dagboek_algemene_klachten_Niezen_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Hoofdpijn_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Algemeen gevoel van ziek zijn_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild)

		2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Koorts of rillingen_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Snotneus_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Neusobstructie_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Keelpijn_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_algemene_klachten_Hoesten_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
Totaal_score_dagboek_algemene_klachten_Totaal score_Dag X		Numeric
pat_dagboek_lage_luchtweg_klachten_Hoesten bij wakker worden_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_lage_luchtweg_klachten_Piepen bij wakker worden_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_lage_luchtweg_klachten_Hoesten overdag_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_lage_luchtweg_klachten_Kortademig overdag_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
pat_dagboek_lage_luchtweg_klachten_Hoesten, piepen of kortademig 's nachts_Dag X	Klachten patiëntendagboek	0 (afwezig) 1 (mild) 2 (matig) 3 (ernstig)
Totaal_score_dagboek_lage_luchtweg_klachten_Totaal score_Dag X		Numeric
(*Y=08:00u,13:00u,18:00u,22:00u)		
Temp_deelnemers_Dag X_Y		Numeric
Uitslag_nasal_swab	Uitslag nasal swab	0=Positive 1=Negative

Lungfunction (*X=0-10,14,25)		
dX_longfunctietest_uitgevoerd	Longfunctietest uitgevoerd	0=Positive 1=Negative
dX_uitleg_longfunctietest_nee		
dX_longfunctietest_uitgevoerd_door		
dX_longfunctietest_ochtend_datum_tijd		
dX_longfunctietest_meting1_metingnummer		numeric
dX_longfunctietest_FVCpred_1		numeric
dX_longfunctietest_FVC		numeric
dX_longfunctietest_FEV1pred		numeric
dX_longfunctietest_FEV1		numeric
dX_longfunctietest_FEV1_FVC		numeric
dX_longfunctietest_PEF		numeric
dX_longfunctietest_duur		numeric
dX_longfunctietest_meting2_metingnummer		numeric
dX_longfunctietest_FVCpred_meting2		numeric
dX_longfunctietest_FVC_meting2		numeric
dX_longfunctietest_FEV1pred_meting2		numeric
dX_longfunctietest_FEV1_meting2		numeric
dX_longfunctietest_FEV1_FVC_meting2		numeric
dX_longfunctietest_PEF_meting2		numeric
dX_longfunctietest_duur_meting2		numeric
dX_longfunctietest_meting3_metingnummer		numeric
dX_longfunctietest_FVCpred_meting3		numeric
dX_longfunctietest_FVC_meting3		numeric
dX_longfunctietest_FEV1pred_meting3		numeric
dX_longfunctietest_FEV1_meting3		numeric
dX_longfunctietest_FEV1_FVC_meting3		numeric
dX_longfunctietest_PEF_meting3		numeric
dX_longfunctietest_duur_meting3		numeric
dX_longfunctietest_kwaliteitsscore_app	Kwaliteitsscore	A,B,C,D,E,F
dX_longfunctietest_kwaliteitsscore_GLI	Kwaliteitsscore	A,B,C,D,E,F

8.2.4 Adverse event

Variable	**Answer option**
Description adverse event	[Free text]
Start date	DD-MM-YYYY
Stop date	DD-MM-YYYY
Severity	Mild / moderate / not related
Relationship to study procedure(s)	Definitely related / possibly related / not related
Action taken	None / discontinued permanently / discontinued temporarily / reduced dose / increased dose / delayed dose

Outcome of adverse event	Resolved, no sequel / AE still present – no treatment / AE still present – being treated / residual effects present – not treated / residual effects presents – treated / death / unknown
Expected	Yes / No
Serious adverse event	Yes / No

8.2.5 Serious adverse event

Variable	**Answer option**
Date of report	DD-MM-YYYY
Date of onset	DD-MM-YYYY
Diagnosis	[Free text]
Event/Reaction	[Free text]
Describe event	[Free text]
Category of serious adverse event	Death / life-threatening / Hospitalization-initial or prolonged / disability/incapacity / congenital anomaly/birth defect / required intervention to prevent all of the aforementioned situations
Relationship to the investigational medicinal product	Unrelated / possible / definite / n/a
If unrelated, was this expected or unexpected	Expected / unexpected
Action taken	None / discontinued temporarily / discontinued / dose temporarily reduced / dose reduced
Outcome of adverse event	Resolved / recovered with sequelae / continuing / resulted in death / unknown
Date event resolved	DD-MM-YYYY
Serious adverse event	Yes / No