Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. N Engl J Med 2016;374:542-54. DOI: 10.1056/NEJMoa1509024

(PDF updated February 17, 2016.)

Adjunctive steroids in HIV-associated cryptococcal meningitis: a randomized controlled trial in African and Southeast Asian countries

Supplementary Material

Contents

Section 1 CryptoDex Investigators List

Dr Eugene Ruzagira MSc[1], Dr Zacchaeus Anywaine MSc[1], Dr Jonathan Kitonsa MBChB[1], Dr Yofesi Nikweri MBChB[1], Dr Ben Masiira MSc[1], Prof Tran Tinh Hien PhD[2,3], Dr Tran Thi Hong Chau PhD[2], Dr Truong Tho Loc MD[2], Ms Van Anh Duong MSc[2], Mr Tuan Lam Thanh MSc[2], Mr Phan Hai Trieu MSc[2], Dr Pham Si Lam MD[2], Dr Thuy Le[2], Dr Nguyen Tat Thanh MD[2], Dr Heiman FL Wertheim PhD[2,3], Prof Nicholas Day DM[4], Dr Phanpaphon Konpan MD[5], Dr Khanungnit Semram MD[5], Dr Prapit Teparrukkul PhD[5], Rungnapa Phanphang BSc[4], Adul Dulsuk BSc[4], Umaporn Kensila MSc[4], Ms Eliana Nyondo RN[6], Ms Grace Kaphale RN[4], Mr Harvey Mafuta CO[4], Mr George Selemani MLT[7], Mr Christopher Kukacha Dip MLT[7], Ms Brigitte Denis MSc[7], Dr A Rizal Ganiem PhD[8], Dr Natriana Tjahjani MD[9], Dr Retno Wahyuningsih PhD[10,11], Dr Sofiati Dian MD[8], Dr Nurul Komari MD[11], Dr Adah Bahri PhD[11], Dr Sucipto Lie MD[11], Dr Gusta T Pratama MScMed[9], Dr Robiatul Adawyah PhD[10,11], Prof Paul Newton DPhil[3,12]

[1] MRC/UVRI Uganda Research Unit on AIDS, Uganda
[2] Oxford University Clinical Research Unit, Wellcome Trust Major Overseas Programme Vietnam, Ho Chi Minh City, Vietnam
[3] Nuffield Department of Clinical Medicine, Centre for Tropical Medicine and Global Health, University of Oxford, UK
[4] Mahidol Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand
[5] Ubon Sappasithiprasong Hospital, Ubon, Thailand
[6] Dignitas International, Zomba, Malawi
[7] Malawi-Liverpool-Wellcome Trust, Clinical Research Programme, Blantyre, Malawi
[8] Hasan Sadikin Hospital, Bandung, Indonesia
[9] RSKO Drug Dependence Hospital, Jakarta, Indonesia
[10] Department of Parasitology, Faculty of Medicine, University of Indonesia, Jakarta
[11] Cipto Mangunkusum Hospital, Jakarta, Indonesia
[12] Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Mahosot Hospital, Vientiane, Laos

Section 2 Study Sites

Country	Site name and level of care	Number of beds and level of care	Number of patients recruited	Authorities providing ethical approval	Authority providing regulatory approval
Vietnam	Hospital for Tropical Diseases (HTD), HCMC.	**550** Tertiary regional referral	79	HTD's IRB AND Ministry of Health's EC	Ministry of Health
	Cho Ray Hospital, HCMC.	**1800** National referral	22	Cho Ray Hospital's IRB AND Ministry of Health's EC	
	National Hospital for Tropical Diseases (NHTD), Ha Noi	**280** National referral	3	NHTD's IRB AND Ministry of Health's EC	
	Bach Mai Hospital, Ha Noi	**1400** National referral	1	Bach Mai Hospital's IRB AND Ministry of Health's EC	
Uganda	Masaka Regional Referral Hospital	**330** Tertiary regional referral	125	Ethics Committee of Uganda Virus Research Institute (UVRI's EC) AND Ethics Committee of the Uganda National Council for Science and Technology (UNCST)	National Drug Authority (NDA)
	Entebbe Grade B Hospital	**100** District hospital	87		
Thailand	Udon Thani Hospital	**924** Tertiary regional referral	45	Local IRB AND Institute for the Development of Human Research Protections (IHRP) AND Ethics Committee of Faculty of Tropical Medicine, Mahidol University (FTMEC)	Not applicable
	Sappasithiprasong Hospital	**1000** Tertiary regional referral	23		
Malawi	Zomba Central Hospital	**600** National referral	35	National Health Sciences Research Committee (NHSRC) AND University of Toronto's EC	Malawi Pharmacy, Medicines & Poisons Board (PMPB)
Indonesia	Cipto Mangunkusum Hospital (RSCM), Jakarta	**600** National referral	13	RSCM-FKUI's EC (EC of Medical Faculty, Indonesia University)	Badan Pengawas Obat dan Makanan (BPOM = FDA)
	RSKO Hospital (Hospital for Drug Independence), Jakarta	**100** National referral	10	RSKO's IRB AND RSCM-FKUI's EC	
	Hasan Sadikin Hospital, Bandung	**900** National referral	3	Hasan Sadikin Hospital's IRB AND RSCM-FKUI's EC	
Laos	Mahosot Hospital, Vientiane	**450** National referral	5	National Ethics Committee for Health Research (NECHR)	Not applicable

Section 3 Lab schedule	**Day 1: Study Entry**	**Day 3**	**Day 7**	**Day 11**	**Day 14**	**Day 21**	**Day 28**	**Day 42**	**Day 70**	**Day 182**
Take informed consent	✓									
Clinical Assessment**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
FBC (Hb, WCC, plt) 1mL	✓		✓		✓					
Na, K, Urea, creat, glu 2 mL	✓	✓	✓	✓	✓	✓#	✓#	✓#		
CD4 / CD8 count 2mL	✓									
HIV antibody 2mL	✓									
Blood cultures 5mL	✓									
CSF Opening pressure	✓	✓	✓		✓	If indicated	If indicated		If indicated	
Lateral Flow Antigen on CSF	✓									
CSF Gram stain, India Ink 0.5mL	✓	✓	✓		✓	If indicated	If indicated		If indicated	
CSF cell count, protein, glucose 1mL	✓	✓	✓		✓	If indicated	If indicated		If indicated	
CSF TB smear 6mL***	✓									
CSF Yeast Quant Count 1mL	✓	✓	✓		✓	If indicated	If indicated			
Store *C. neoformans* isolate****	✓									
Store CSF supernatant and pellet	✓	✓	✓		✓	If indicated	If indicated		If indicated	
Sputum TB smear*****	✓									
Chest X-ray***	✓									
Store blood plasma 4.5mL	✓									
Store blood cell pellet	✓									
Approximate blood volume mL	16.5	2	3	2	3	3	3	2		
Approximate CSF volume mL	8.5	2-5	2-5		2-5					

* Study drug is given daily from day 1 – day 42

** GCS Assessment is daily while an in-patient. When outpatient assessment can take place at the scheduled time + up to 5 days (eg 4 week assessment on day 28-33). Day 182 assessment may be by telephone.

***Optional if local resources are unavailable

****Also store any isolate where the quantitative culture assessment is higher than the previous assessment or relapse case

***** Perform sputum smear if patient can produce a sample

glucose only

NB: Blood volumes are estimates

Section 4 Grading outcome and disability with the "Two simple questions" and Rankin score

The worst outcome from the two following tests was used for analysis

The two simple questions

1. Does the patient require help from anybody for everyday activities? *(For example eating, drinking, washing, brushing teeth, going to the toilet.)*

2. Has the illness left the patient with any other problems?

Question 1 answered "yes": poor outcome. Question 2 answered "yes": intermediate outcome. If both questions are answered "no": Good outcome.

The Modified Rankin Scale

Grade	**Description**
0	No symptoms
1	Minor symptoms not interfering with lifestyle
2	Symptoms that lead to some restriction in lifestyle, but do not interfere with the patients' ability to look after themselves
3	Symptoms that restrict lifestyle and prevent totally independent living
4	Symptoms that clearly prevent independent living, although the patient does not need constant care and attention
5	Totally dependent, requiring constant help day and night

Grade 0: Good outcome, Grade 1 or 2: Intermediate outcome, Grade 3-5: poor outcome

Statistical analysis plan for the CryptoDex study (ISRCTN59144167)

"Adjunctive dexamethasone in HIV-infected adults with cryptococcal meningitis"

Authors: Marcel Wolbers, Nhan Ho Thi, Justin Beardsley, Jeremy Day

Version: 1.00, 25Mar2015 (final version before unblinding of the trial)

This version: 1.11, 10April2015 with changes and additional analyses performed after unblinding added in blue.

Purpose

This document details the planned analyses and endpoint derivations for the ISRCTN59144167 trial as outlined in the published study protocol (Day et al., Trials 2014, 15:441, doi:10.1186/1745-6215-15-441). It focuses on the analysis for the main clinical trial publication and does not include analysis for any subsidiary studies.

Statistical software

Data derivations will be performed with the statistical software SAS v9.2 (SAS Insitute, Cary, North Carolina, US). All statistical analyses will be performed with the statistical software R using the current R version at the time of the final analysis (R Foundation for Statistical Computing, Vienna, Austria).

Interim analyses and early stopping of the trial

Interim analyses for this trial were conducted by an independent statistician and reviewed by the Data Monitoring and Ethics Committee (DMEC) after approximately every 50 deaths as detailed in the study protocol, the DMEC charter, and the interim analysis plan.

The DMEC reviewed the data of the third interim analysis (including 411 subjects and 172 deaths) on August 15, 2014, and recommended in a formal letter to the investigators on August 29, 2014, to stop the trial because of evidence that adjunctive treatment with dexamethasone is harmful.

Based on this recommendation, recruitment of the trial was suspended on the same day (August 29, 2014) and a teleconference between study investigators and the trial steering committee (TSC) was held on September 2, 2014, where it was decided that treatment of patients still on randomized treatment would be tapered and that the study statistician and the TSC would also review the unblinded data before a final decision was made. Based on the unblinded results, the TSC suggested unanimously to adopt the DSMB recommendation and recruitment was formally stopped on September 12, 2014. However, follow-up of the study was continued and blinding was maintained until all recruited subjects completed the planned 6 months of follow-up.

Formal adjustment of the statistical analysis for early stopping would be impossible as the decision to stop due to suggested harm was not based on formal crossing of a stopping boundary but on an overall clinical assessment of the data. Therefore, all reported confidence intervals and p-values outlined in this statistical analysis plan will be the "usual" values without any attempt to adjust them for interim analyses.

Analysis populations

Intention-to treat population (ITT)

The primary analysis population for all analysis is the full analysis population containing all randomised patients except for those mistakenly randomised without cryptococcal meningitis [no known patients] and patients who did not receive the allocated treatment because of an administration error [1 patient, 63-001]. Patients not receiving any study treatment will still be included in the ITT. Patients will be analysed according to their randomized arm (intention-to-treat).

Per-protocol population

The primary end point will also be analysed on the per-protocol population, which will exclude the following patients: major protocol violations and those receiving less than 1 week of administration of the randomised study drug for reasons other than death.

Subjects randomized <6 weeks before 02Sep2014 (i.e. those who were subject to tapering of the study drug as a result of stopping the trial) will be censored on 02Sep2014 in the per protocol analysis.

Derivation rules for the definition of study populations:

- The following will be considered as "major protocol violations":
  - Pregnancy: 1 patient [65-061] for whom the pregnancy is recorded as an USAE
  - Less than 1 week of amphotericin B antifungal therapy after randomization for reasons other than death (interpreted in the same way as for the study drug, see below). Amphotericin B antifungal therapy is recorded on the concomitant medication (CONMED) form and as drug names are not entirely consistently reported, amphotericin B will be identified as any drug name containing the string "AMPHO".
- Less than 1 week of administration of the randomised study drug for reasons other than death:
  - To allow that study drug is stopped up to 3 days prior to death, this will be interpreted as receiving <7 days of study drug for those who did not die within the first 9 days and as receiving less than [day of death]-3 doses of study drug for those who died earlier (i.e. <6 doses for patients who die on day 9, <5 doses for patients who die on day 8, …, no study drug at all for patients who die on days 1-4) .

Baseline characteristics

Baseline characteristics will be summarized as median (IQR) for continuous data and n(%) for categorical data. The amount of missing data for each baseline characteristic will also be displayed.

Formal comparisons of baseline characteristics between study arms are discouraged by most statisticians (see e.g. Senn SS (2008): Statistical Issues in Drug Development, 2nd Edition, Wiley [p. 98f]) but mandated by some journals. To satisfy all potential publishers, we will calculate p-values (based on the Wilcoxon rank sum test and Fisher's exact test for continuous and categorical data, respectively) but will only report them if mandated by the journal.

Baseline/date of randomization is defined as the date of the first dose of study treatment (first DateGiven in dataset MED). If a subject did not receive any study treatment at all, baseline will be defined as the date of the baseline (history and examination) assessment (BASE.DateAss).

The following baseline characteristics will be summarized by treatment arm [with derivation rules in brackets]:

BASE: BASELINE – HISTORY AND EXAMINATION

All recorded variables in the BASE form with the following modifications:

- Site, country and continent will also be summarized
- Free text specifications will not be summarized.
- If dates are given (e.g. date of birth, prior HIV diagnosis, or prior cryptococcal meningitis), the time from that date to baseline will be summarized rather than the date.
- For fluconazole prophylaxis: only yes/no, not the duration will be summarized
- For any antifungal treatment for THIS CURRENT diagnosis of cryptococcal meningitis BEFORE randomization: Only the given antifungals (yes/no), whether it was fluconazole monotherapy (yes/no) and the maximum recorded days on any prior antifungal treatment will be reported.
- Other Opportunistic Infection Prophylaxis up to this admission: Only the given drugs (co-trimoxazole, isoniazid, and/or other) will be summarized.
- GCS will also be summarized as a categorical variable with values ≤10, 11-14, and 15.
- For visual acuity, the worst result of both eyes will also be summarized.
- Cranial nerve palsies (CNP) will be summarized as “CNP 6” [CNPLeft6 or CNPRight6 ticked], “Other CNP” [at least one CNP other than CNP 6 ticked] , “None” [CNPnone ticked] or “Unable to assess” [CNPUnable ticked].

HEMA (LABORATORY TEST RESULTS – HEMATOLOGY), CHEMIS (LABORATORY TEST RESULTS – CHEMISTRY), microbiology (MICRO) and HIVFU (CD4 and CD8)

- Baseline results for all values (with proper unit conversion) will be recorded. If no values are available before or at enrolment, values up to 1 day post enrolment will be used as baseline values for hematotology, chemistry, and values up to 14 days post enrolment will be imputed as baseline values for CD4 and CD8. (The latest CD4 value recorded on the Base form will also be included in this derivation as long as it did not occur >3 months (91 days) prior to enrolment.) For chemistry, blood glucose values recorded on the lumbar puncture form will also be included in the derivation.
- For microbiology tests, the baseline test result will be summarized as "positive" if at least one positive test result was recorded up to 3 day post enrolment, and "negative" if at least one negative and no positive test result was recorded.

LP (LUMBAR PUNCTURE)

- Baseline results for the following values (with proper unit conversion, if necessary) will be recorded: Opening and closing pressure, WCC, % of lymph, % of neut, % of mono, % of eosin, protein, CSF glucose, CSF/blood glucose ratio), and yeast quantitative count. If no values are available at or before enrolment, values up to 1 day post enrolment will be imputed as baseline values. For the calculation of the CSF/blood glucose ratio, missing blood glucose values on the lumbar puncture form will be imputed with the blood glucose value recorded on the chemistry form if that value is from the same day as the CSF glucose value.
- Test results for microbiology CSF tests, the baseline test result will be summarized as "positive" if at least one positive test result was recorded up to 3 day post enrolment, and "negative" if at least one negative and no positive test result was recorded.

IMAGING (XRAY and BRAINSCAN)

- The number of patients with a chest Xray, a brain MRI, or a brain CT at baseline (allowing -7/+2 days) and the respective numbers of abnormal findings for each imaging method will be summarized.

Planned analyses

Baseline table for all variables as detailed above for the ITT population. The main summary is by treatment group but an additional descriptive summary by continent will also be created.

Primary endpoint – overall survival until 10 weeks after randomisation

Derivation of overall survival until 6 months after randomisation

Definition of time to death: [date of death or censoring]-[date of randomization]+1

Definition event indicator: =1 if patient died =0 otherwise

[Date of randomization]:

Date of first dose of study treatment (first DateGiven in dataset MED). If a subject did not receive any study treatment at all, baseline will be defined as the date of the baseline (history and examination) assessment (BASE.DateAss).

[Date of death]:

Final status is death (FINAL.status=2) and the corresponding date of death is FINAL.Datedeath.

[Date of censoring]:

If a final status form is available for the patient (which should be the case for every patient at completion of the study) then the date of censoring is defined as the date of study completion (FINAL. DateFinalCon) or, if the patient did not complete the study, the date of last contact (FINAL.DateLastCon).

If the patient is still under follow-up, i.e. no final status form is available, the date of censoring is defined as the last recorded date of an inpatient or outpatient assessment, the week 10 or month 6 visit, a GCS, hematology, or blood chemistry date, or a study drug administration date.

Note: The date of the actual visits will be used in the calculations. However, subjects who were followed up for >200 days or died after day 200 will be treated as censored on that day instead. Importantly, all patients died before day 183 according to the final blinded database, i.e. the analysis is not sensitive to the choice of the cut-off. The 200 day cut-off, which was chosen to report all relevant events even if they occurred slightly after the strict 6 month cut-off, will also be applied to all other time-to-event outcomes.

Derivation of overall survival until 10 weeks after randomisation

The derivation of the primary endpoint is based on the derivation of overall survival as described above. All subjects with follow-up or death after day 71 will be treated as censored on day 71.

Planned analyses for the primary endpoint

Primary analysis

The analysis will be based on a stratified Cox proportional hazards model allowing for separate baseline hazards for each continent (Asia or Africa) and treatment allocation as the only covariate. The stratification is based upon the expectation of different mortalities in the control arm by continent but similar (relative) effects of the intervention across continents. The proposed test is essentially equivalent to using a stratified log-rank test to compare the two treatment arms. We prefer to use the Cox model as it automatically provides treatment effect estimates and confidence intervals in addition to the P value.

Stratified Cox regression as implemented in the R function survival::coxph will be used with default arguments (e.g. tie handling according to the Efron approximation).

The proportional hazards assumption will be formally tested based on scaled Schoenfeld residuals and visually assessed by a plot of the scaled Schoenfeld residuals versus transformed time (as implemented

in R function survival::cox.zph). In case of a significant test, a formal comparison of 10-week survival probabilities between the two groups will also be performed (using Kaplan-Meier estimation and Greenwood's formula to approximate variance).

Kaplan-Meier estimates of the survival curve by treatment arm [for overall survival until 6 months after randomisation]

- Plots for all subjects and for each continent separately
- Explicit numeric estimates (with 95% CI) at 10 weeks and 6 months

Cox regression

- Stratified by continent and including the following covariates (in addition to the treatment group): country, baseline fungal load, Glasgow coma score less than 15 (yes/no), and ART status at study entry (on ART at enrolment: no/ yes but ≤ 3 months/ yes, > 3 MONTHS).

Pre-defined subgroup analyses

The following subgroups are pre-defined:

- Continent
- Country
- IDSA indications for steroid treatment at baseline:
  - Cryptococcoma with mass effect (yes/no) - yes, if there's a CT/MRI showing cryptococcoma at baseline (allowing -7/+2 days) (BRAINSCAN)
  - Acute respiratory distress syndrome (yes/no) – yes if baseline question 18c is answered yes

  Note: These were pre-defined subgroup analyses but no CT/MRI showed cryptococcoma and only 3 patients had acute respiratory distress syndrome according to the final blinded data base. Hence these subgroup analyses will be omitted.
- Unmasking IRIS: this is covered by the subgroup analysis by ART status, see below

- Glasgow coma score <15 (yes/no)
- On ART at enrolment (no/ yes but ≤ 3 months/ yes, > 3 MONTHS)
- Per protocol analysis – yes
- *Sex*
- *Age (≤35 vs. >35 years)*
- *Quantitative fungal count at enrolment (<10^5 cells/ml, ≥10^5 cells/ml CSF)*
- *CD4 cell count (≤25 vs. >25 cells/mm3)*
- *Subjects randomized ≥6 weeks before 02Sep2014 (subjects randomized later were subject to tapering of the study drug)*
- *Opening pressure >18 at baseline* (yes/no)
- *CSF WCC <5 at baseline* (yes/no)

Note: Subgroups in *italic* are not pre-defined in the protocol but are added as pre-defined subgroup analysis in this analysis plan.

Potential heterogeneity of the treatment effect across sub-groups will be tested using likelihood ratio tests for an interaction term between treatment and the grouping variable.

Other exploratory analysis

Will be performed as appropriate.

Note (added after unblinding): As the analyses showed clear evidence of non-proportional hazards of the treatment effect, the hazard ratio (HR) in different time-period was also reported. Specifically, we decided to split the first 10 weeks into the first half of dexamethasone treatment (weeks 1-3), the second half (weeks 4-6), and the time thereafter (weeks 7-10) and reported the HR in each time interval as an exploratory analysis.

Treatment of missing values (multiple imputation)

Multiple imputation by chained equations as implemented in the R package mice will be used to deal with missing covariate values for the Cox regression analysis. Specifically, 20 imputed sets will be generated and the dataset for multiple imputation will include the following variables:

- Baseline variables: continent, country, age, sex, GCS, on ART at study entry (no/ yes but ≤ 3 months/ yes, > 3 MONTHS), CD4 cell count
- CSF measurements: opening pressure and yeast quant counts at baseline, day 3, day 7 (+/-1 day), and 14 (+/-2 days) [both log-transformed]
- Outcomes: overall survival until 10 weeks after randomization, overall survival until 6 months after randomization, neurological disability at 10 weeks and 6 months.

Time-to-event outcomes (i.e. overall survival) will be included as the cumulative (cause-specific) baseline hazard at the observed event or censoring time and an event indicator as recommended by White and Royston (Statist. Med. 2009; 28:1982–1998).

Secondary endpoint – Survival until 6 months after randomization

The derivation is outlined above and the planned analyses are the same as for the primary endpoint.

Secondary endpoint – neurological disability at 10 weeks and 6 months

Derivation

The disability score was assessed at week 10 and month 6 of follow-up and both assessments will be separately analyzed as co-secondary endpoint.

The score is composed of two sub-scores:

The “two simple questions” score [NeedHelp and AnyProblem in datasets WEEK10 and MONTH6]:

If answer to the first question= yes; outcome is classified as ‘severe disability’

If answer to the second question = yes; outcome is classified as ‘intermediate’

If answer to both questions = no; outcome is classified as 'good'

The modified Rankin score: [ModRanScore in datasets WEEK10 and MONTH6]

If Rankin score=1; outcome will be classified as 'good'

If Rankin score =2 or=3; outcome will be classified as 'intermediate'

If Rankin score =4, =5 or=6; outcome will be classified as 'severe disability'

[Note that the Rankin scale is coded as taking values from 1-6 on the database, i.e. +1 compared to the levels 0-5 according to the published study protocol.]

The worst disability outcome from either questionnaire ("two simple questions" or Rankin score) will be used for analysis. Disability will be defined as "death" if the patient died before the scheduled time point.

Planned analysis

The proportion of patients with a good outcome will be compared between the two arms with a logistic regression adjusted for continent (in addition to the treatment arm). Both a complete case analysis (which treats patients lost to follow-up without a disability assessment as missing) and an analysis based on multiple imputation of missing values will be performed (see section "Treatment of missing values (multiple imputation)" above for details regarding the imputation).

The analysis will be performed in all patients (ITT), in the per protocol population, by continent, and according to the baseline Glasgow score (<15 vs. 15).

Secondary endpoint – Rate of CSF sterilisation during the first 2 weeks (based on available data from all sites)

Planned analysis

All recorded longitudinal quantitative fungal count measurements up to day 17 (allowing for some delays in the day 14 measurements) will be included in the analysis. Fungal decline will be modeled with a joint model for longitudinal and survival data. The longitudinal part of the model will be a linear mixed-effects model with longitudinal log-CSF quantitative culture fungal counts as the outcome, continent and interaction terms between the treatment groups and the time since enrolment of the measurement as fixed covariates, and a random patients-specific intercept and slope. The survival part of the joint model models mortality up to 10 weeks depending on the treatment group, continent, and the patient-specific random intercepts and slopes. The survival part acts as a missing data mechanism to allow potentially informative truncation of quantitative count measurements due to death. Of note, the protocol specified that we will include only 2-week survival in the joint model but as 10-week survival is the primary outcome of the study and we would also like to assess the impact of the rate of CSF sterilization on the primary outcome, we decided prior to unblinding of the study to use 10-week survival in the joint model instead.

The lowest measurable quantitative count is 5 and values below the detection limit (which correspond to recorded values of 0) will be treated as <4.5 cells/ml, i.e. non-detectable measurements will be treated as left-censored longitudinal observations in the analysis.

The joint model will be implemented with the R package JMBayes version 0.7-0 which allows to appropriately handle detection limits for longitudinal measurements. In case MCMC diagnostics plots of the fitted JMBayes models indicate failure of the algorithm we will report results from a mixed model with a detection limit (but ignoring truncation by death) instead and this will be implemented using vague priors in the software JAGS. In addition, results from a conventional mixed model ignoring the detection limit will also be calculated for comparison purposes to earlier publications where this has been reported.

The analysis will be performed in all patients (ITT), by continent, and by quantitative fungal count at enrolment (<10^5 cells/ml, ≥10^5 cells/ml CSF).

Note (added after unblinding): When applied to our data, the R package JMBayes v0.70 (with default settings) did not provide reliable results. Specifically, if left-censoring was ignored (and hence alternative methods were available), results from JMBayes were highly discrepant from the results of another joint modeling package in R (package JM v1.30) and a simple linear mixed effects model whereas the latter two approaches gave very similar results which also were in much better agreement with visual displays of longitudinal fungal counts.

Therefore, it was decided that the rate of fungal declines will be reported based on a Bayesian longitudinal model allowing for a detection limit which was implemented using JAGS v3.4.0. Specifically, the model was based on a fixed intercept, a fixed treatment-specific slope, and patient-specific random intercepts and slopes with vague priors: Normal priors with mean 0 and variance 100 for the fixed effects, a scaled inverse Wishart distribution for the covariance matrix of the random intercept and slope, and a uniform prior from [0,100] for standard deviation of the residual error. Log10-CSF quantitative culture fungal counts below the detection limit were treated as left censored at log10(4.5) as discussed above. Reported "95% confidence intervals" correspond to Bayesian 95% credible intervals and the reported "p-values" refer to crude "Wald-type" tests of the mean estimate divided by its standard deviation.

Secondary endpoint – Rate of IRIS until 10 weeks

Derivation

The derived endpoint will be the competing risks endpoint of the time to first IRIS or death defined as:

Time to event=[date of first IRIS event or death or censoring]-[date of randomization]+1

Event type:

0/"censored": if patient is censored (no IRIS events or death recorded)

1/"IRIS": if patient had an IRIS event (any adverse event recorded as IRIS)

2/"prior death": if patient died without prior IRIS

Two endpoints will be derived: First, the endpoint including all available follow-up (6 months) and a derived second endpoint which is censored on day 71 (week 10).

Planned analysis

The rate of IRIS will be modeled with a proportional cause-specific hazards model with treatment as the only covariate and stratification by continent, taking into account the competing risk of prior death. The analysis will also be done separately by continent. The main analysis is for the 10 week outcome and the 6 month outcome is a supplementary analysis.

Non-parametric estimates of the cumulative incidence functions for the two competing events (IRIS and prior death) will also be calculated and displayed by treatment arm (including 6 months of follow-up).

Secondary endpoint – Time to new AIDS-defining illnesses or death until 10 weeks

Derivation

The derived endpoint will be the competing risks endpoint of the first new AIDS event or death defined as:

Time to event=[date of first AIDS event or death or censoring]-[date of randomization]+1

Event type:

0/"censored": if patient is censored (no AIDS events or death recorded)

1/"AIDS": if patient had an AIDS event (any adverse event recorded as new AIDS defining illness)

2/"prior death": if patient died without a prior new or recurrent AIDS-defining illness

Two endpoints will be derived: First, the endpoint including all available follow-up (6 months) and a derived second endpoint which is censored on day 71 (week 10).

Planned analysis

Stratified Cox regression (by continent) of the composite endpoint. The analysis will also be done separately by continent. The main analysis is for the 10 week outcome and the 6 month outcome is a supplementary analysis.

Secondary endpoint – Visual deficit at 10 weeks

The visual acuity at 10 weeks is recorded on a 6 point scale as defined in the protocol and will be summarized by treatment arm for each eye separately, and overall where "overall" is defined as the worst recorded acuity of either eye. The fundoscopy result at 10 weeks will also be summarized by treatment arm as "Normal", "Abnormal", or "Unable to visualize fundus".

Statistical comparisons between treatment arms are complicated by the fact that visual assessments are only available in survivors which might introduce selection bias. Nevertheless, the odds of having "normal acuity" and "normal fundoscopy" (amongst all surviving patients with a visual assessment) will be compared between the treatment arms with a logistic regression model adjusted for continent.

Secondary endpoint – Time to new neurologic event or death until 10 weeks

Derivation

The derived endpoint will be the competing risks endpoint of the time to first new neurological event or death defined as:

Time to event=[date of first neurological event or death or censoring]-[date of randomization]+1

Event type:

0/"censored": if patient is censored (no neurological event or death recorded)

1/"NNE": if patient had an new neurological event (defined below)

2/"prior death": if patient died without a prior new neurological event

Neurological events are defined as any grade 3 or 4 new neurological events or any fall in GCS ≥2points, for ≥48hrs (which will also be programmed separately based on recorded longitudinal GCS).

Two endpoints will be derived: First, the endpoint including all available follow-up (6 months) and a derived second endpoint which is censored on day 71 (week 10).

Planned analysis

As for the endpoint "time to new AIDS-defining illnesses or death until 10 weeks" (see above).

Secondary endpoint – Longitudinal measurements of intracranial pressure during the first 2 weeks

This endpoint will be modeled in the same way as longitudinal quantitative counts except that there is no detection limit for intracranial pressure. See the section "Secondary endpoint – Rate of CSF sterilisation during the first 2 weeks" for details.

Secondary endpoint – Relapse (Antifungal treatment intensification or retreatment for cryptococcal meningitis) in the 6 months after randomization

As for the endpoint "Rate of IRIS until 10 weeks" (see above) except that only the 6 month outcome will be analysed.

Relapses are defined as described in the protocol and recorded as new AIDS-defining illnesses with adverse event name "Cryptococcal meningitis relapse".

Secondary endpoint – Clinical adverse events and new laboratory adverse abnormalities

Derivation

Adverse events (AE) are all events recorded on the NEW NEUROLOGICAL EVENT (NNE), NEW AIDS DEFINING ILLNESS (NADI), IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS), or OTHER ADVERSE EVENT (OAE) forms. All grade 3&4 AE were collected and also considered as SAE (serious adverse events); grade 1&2 AE where only collected for NNE, NADI, and IRIS events but not OAE.

New laboratory abnormalities are defined as any worsening of a lab value to grade 3 or 4 (including changes from grade 3 to 4) compared to the subject's previous lab value. In addition, to be conservative, if a subject's baseline lab value was missing, the worst post-enrolment lab value was also be considered a new lab abnormality if it was of grade 3 or 4. A grading table for laboratory abnormalities is provided in the Appendix.

Planned analysis (by treatment group)

- Summary of all reported AE – overall and by continent (separate summaries by type only and by type and subtype will be produced)
- Summary of all grade 3&4 AE – overall and by continent
- Summary of grade 3&4 AE with onset within the first 6 weeks by type
- Summary of grade 3&4 AE with onset during weeks 6-10
- Summary of grade 3&4 AE with onset after weeks 10
- Summary of total number of grade 3&4 AE per patient
- Summary of new laboratory abnormalities

Additional planned auxiliary analyses

- Summary of time to ART initiation:
  - Categorized outcome: On ART at study entry/ART started after study entry/No ART documented.
  - Median (IQR) time to ART initiation in those who started ART after study entry.
  - Details for subjects with no ART documented: Subject died within <42 days without ART/ subject died after >=42 days without ART/ subject alive but no ART documented.
- Number of chest X-rays, CT scans and MRI performed after baseline and proportion with an abnormal result.
- Summary whether study drug was terminated before 6 weeks (for reasons other than death) by treatment group – based on tickbox on final status form
- Summary of the number of days of Amphotericin B treatment after enrolment

Grading of laboratory abnormalities

	Grade 3	**Grade 4**

Haematological		
Haemoglobin	6.5 –7.9g/dl	<6.5 g/dl
White cell count	1.0 - 1.9 K/μl or g/L	<1.0 K/μl or g/L
Neutrophils	NEU % xWBC=NEU K/μl :0.5 – 1.0 K/μl	NEU % xWBC=NEU K/μl <0.5 K/μl
Platelets	25 – 50 K/μl or g/L	<25 K/μl or g/L
Biochemical		
Sodium - HYPONATRAEMIA	120-130 mmol/l	<120 mmol/l
Sodium - HYPERNATRAEMIA	155 – 160 mmol/l	>160 mmol/l
Potassium	2.5 – 3.0 mmol/l	<2.5 mmol/l
Potassium	6.0 – 7.0 mmol/l	>7.0 mmol/l
Blood glucose	1.7 – 2.2 mmol/l or 30-40 mg/dl 13.9-27.8 mmol/l or 250-500 mg/dl	<1.7 mmol/l or < 30 mg/dl >27.8 mmol/l or >500 mg/dl
Creatinine	>3X BASELINE OR 3-6 X ULN	>6X ULN
AST	>5-20-X ULN	>20X ULN
ALT	>5-20-X ULN	>20X ULN

ULN for Creatinine: 1.36 mg/dL (males), 1.13 mg/dL (females)

ULN for AST/ALT: 40 IU

Data Monitoring and Ethics Committee

CHARTER

Data Monitoring and Ethics Committee (DMEC) Overview

Trial Description and Study Design

- Trial sponsor: University of Oxford
- Trial design: Randomized double-blind placebo controlled multi-centre clinical trial of dexamethasone in HIV associated cryptococcal meningitis
- Number of patients: 880
- Names of sites:

#	Country	City	Name of site
1	Viet Nam	Ho Chi Minh	Hospital for Tropical Diseases
2	Viet Nam	Ho Chi Minh	Cho Ray Hospital
3	Viet Nam	Hanoi	National Hospital for Tropical Diseases
4	Viet Nam	Hanoi	Bach Mai Hospital
5	Thailand	Udon Thani	Udon Thani hospital
6	Thailand	Ubon Sappasithiprasong	Ubon Sappasithiprasong Hospital
7	Lao	Vientiane	Mahosot Hospital
8	Indonesia	Jakarta	Cipto Mangunkusum Hospital
9	Indonesia	Jakarta	RSKO (Hospital for Drug Independence)
10	Indonesia	Bandung	Hasan Sadikin Hospital, Bandung
11	Malawi	Zomba	Zomba Central Hospital / Malawi-Liverpool-Wellcome Trust Clinical Research Programme
12	Uganda	Entebbe	Entebbe Grade B Hospital / MRC/UVRI Uganda Research

			Unit on AIDS
13	Uganda	Masaka	Masaka Hospital / MRC/UVRI Uganda Research Unit on AIDS

- Principal Investigator: **Dr. Jeremy Day**

DMEC Terms of Reference (from MRC Guidelines of Good Clinical Practice in Clinical Trials 1998)

1. To determine if additional interim analyses of trial data should be undertaken
2. To consider the unblinded data from interim analyses, plus additional safety measures for the above named trial and relevant information from other sources
3. In the light of 2., and ensuring that ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee and to recommend on the continuation of the trial
4. To consider any requests for release of interim trial data and to recommend to the TSC on the advisability of this
5. In the event of further funding being required, to provide to the TSC and MRC appropriate information and advice on the data gathered to date that will not jeopardize the integrity of the study.

DMEC Membership

- This charter will be agreed by all DMEC members.
- Composition of membership will be:

  Dr Diederik van de Beek – DMEC Chairman - clinician and neurology specialist, Department of Neurology, Amsterdam Medical Centre

  Dr Ronald B Geskus – Biostatistician - Department of Clinical Epidemiology, Biostatistics and Bioinformatics, University of Amsterdam

  Professor Janet Darbyshire, Emeritus Professor of Epidemiology, UCL, London

  Professor David Mabey, Professor of Communicable Diseases, London School of Hygiene and Tropical Medicine

  Dr. Andrew Kambugu, Head of the Research Programme at the Infectious Disease Institute (IDI), Makerere University College of Health Sciences

Acronyms

CTU – Clinical Trials Unit (of OUCRU-VN)

DMEC – Data Monitoring and Ethics Committee

MRC – Medical Research Council, UK

OUCRU-VN – Oxford University Clinical Research Unit – Viet Nam

PI – Principal Investigator

TSC – Trial Steering Committee

Introduction

The purpose of this charter is to define the roles and responsibilities of the Data Monitoring and Ethical Committee (DMEC), delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.

The DMEC will function in accordance with the MRC guidelines for Good Clinical Practice in Clinical Trials and the approved trial protocol.

The DMEC administration will be coordinated by the OUCRU-VN Clinical Trials Unit. All significant communications, meetings and reports will be made in writing, communicated to all relevant parties and maintained with the Trial Master File.

Definitions

The following definitions apply to this protocol:

Ethical Committee of Reference: the lead ethical committee to which all safety reporting and DMEC reports are issued. In the case of this trial, the ethical committee of reference is the Oxford Tropical Research Ethics Committee.

Grade 3 or 4 Adverse Event: any untoward medical occurrence of severity defined as grade 3 or 4 by the Common Terminology Criteria for Adverse Events from National Cancer Institute (CTCAE)

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

For the purpose for this trial, the following events will be classified as grade 4 events:

- repeated culture of *C. neoformans* from CSF or blood after previous sterilization (grade 4)
- confirmed diagnosis of a new or reoccurring opportunistic infection (grade 4 if life threatening, grade 3 if requires treatment)

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

- results in death
- is life threatening
- requires unplanned inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or is a congenital anomaly/ birth defect

Unexpected Serious Adverse Event (USAE): Untoward medical events which fit one or more criteria of SAE above and which are not considered a part of normal clinical progression of disease or expected drug reaction. Any event which becomes of concern to the investigators or study doctors during the course of the trial may be reported as a USAE.

Roles and Responsibilities

DMEC Roles and Responsibilities

This DMEC will

- Receive, review and feedback when necessary on blinded USAEs reported in detail within 2 weeks of occurrence and followed until resolution
- Meet periodically (see DMEC Meetings) to review unblinded summary tables of serious adverse events (SAEs), grade 3 & 4 AEs, estimates of 14-day killing rates of yeast by treatment arm from selected sites and analysis of overall survival. The DMEC may request additional data as required including aggregate and individual subject data related to safety, data integrity and overall conduct of the trial.
- Provide recommendations to continue, modify or terminate the trial depending upon these analyses.
- Communicate other recommendations or concerns as appropriate including requests for additional unblinded reviews based on regular reporting and USAE reporting.
- Comply with and operate according to the procedures described in this charter.
- Maintain documentation and records of all activities as described below (see DMEC Chairman, DMEC Meetings, DMEC Reports).

DMEC Chairman will

- Be responsible to archive the interim analysis reports and documentation of rationale for decisions made by the Committee during closed sessions. These will be provided to the Principal Investigator upon completion of the trial.

DMEC Statistician will

- Generate the analysis tables and distribute the interim report amongst the DMEC members as described below (see section “Creation of interim analysis reports” below).

Principal Investigator Roles and Responsibilities

The PI will directly or through delegation:

- Assure the proper conduct of the study including collection of accurate and timely data.
- Compile and report USAEs as described below.
- Promptly report potential safety concern(s) to the DMEC.
- Communicate with regulatory authorities, ethical committees and investigators, in a manner that maintains patient safety and integrity of the data.

DMEC Participation

Membership will be selected by the Principal Investigator and approved by the Joint Global Health Trials administrative representative. If a DMEC member is unable to continue participation on the committee, the reason will be documented and a replacement will be selected by the Principal Investigator with the agreement of the other DMEC members and endorsement of the Trial Steering Committee and the Joint Global Health Trials administrative representative.

DMEC members will declare any existing or potential conflicts of interest to the Principal Investigator who will report to the Joint Global Health Trials administrative representative. Conflicts of interest will be reduced to the greatest extent that is consistent with assembling a highly competent DMEC. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DMEC Chair (or in the case of the Chair having a conflict, by the Trial Steering Committee Chair) and the Joint Global Health Trials administrative representative as necessary.

A conflict of interest exists or potentially exists when a member has a personal, professional or financial interest which could unduly influence the member's position with respect to the trial or trial related issues. A conflict of interest should also be addressed if an interest could result in the member's objectivity being questioned by others.

DMEC Meetings

Projected Schedule of Meetings

Correspondence with the DMEC will be initiated by the OUCRU Clinical Trials Unit prior to any subject enrollment in the trial in order for the members to review the charter, to form an understanding of the protocol, agree to the safety reporting procedures, to establish a meeting schedule and to review the study modification and/or termination guidelines. Subsequent interim and final review meetings will be held to review and discuss interim and final study data according to the schedule below. Meetings will occur at least annually and additional meetings may be scheduled at the request of the DSMC Chairman, the Trial Steering Committee or the sponsor.

Timeline	***Data Review by***	***Type of Data***
At study initiation	Entire DMEC	Study protocol, safety concerns, DMEC Charter and associated procedures/reports
After the death of 50 enrolled patients or after the enrolment of 200 patients – whichever comes first	Entire DMEC	USAE or event reports submitted to the DMEC Enrolment summary Unblinded tables of grade 3 & 4 AEs and SAEs 14-day killing rates of yeast by treatment arm from selected sites Overall survival analysis Any other requested data
After the death of 100 enrolled patients	Entire DMEC	Same as above.
After the death of every additional 50 enrolled patients	Entire DMEC	Same as above.

Meeting Format

DMEC meetings will generally be conducted by teleconference and coordinated by the administrative coordinator named above. A quorum, defined as a minimum of 3 members will be required to hold a DMEC meeting. Any one member may be absent provided that they are sent the relevant data at least 3 days in advance of the meeting and given opportunity to feedback to other members. Critical decisions of the DMEC should be made by unanimous vote. However, if this is not possible, majority vote will decide. When appropriate DMEC review sessions may be held by email exchange in lieu of a meeting.

Open and Closed Sessions

Sessions may be open (attended by representatives of the sponsor and study team) or closed (attended only by DMEC members) at the direction of the DMEC. All data presented at the open sessions must be blinded. A report based on each DMEC meeting will be organized by Chairman and submitted to the Trial Steering Committee. This report will include a recommendation to:

- Continue the trial without modification
- Continue the trial with modification
- Stop the trial due to safety concerns
- Stop the trial for another reason

Reports will be circulated to all DMEC members for their approval before being issued.

Creation of interim analysis reports

The study statistician will generate the code (in the statistical software R) to generate all tables outlined in the Interim Analysis Plan but will remain blinded to the treatment assignment throughout the study.

Prior to each interim analysis, raw data will be transferred from the study statistician to the DMEC statistician together with R code to generate all summary tables. A separate file with the randomization code will be transferred from the pharmacist managing the randomization list to the DMEC statistician. Based on this information, the DMEC statistician will merge the randomization code to the data, generate the tables and distribute the interim report amongst the DMEC members.

Conduct of interim analyses

Raw data will be transferred from the study statistician to the DMEC statistician together with R code to generate all summary tables as specified in this analysis plan. A separate file with the randomization code will be transferred from the pharmacist managing the randomization list to the DMEC statistician.

Based on this information, the DMEC statistician will merge the randomization code to the data, generate the tables and distribute the interim report amongst the DMEC members.

Study Review Criteria, Stopping Rules and Guidelines

Safety Analyses

The primary safety endpoint is survival. In addition to the primary safety endpoint, the DMEC will consider grade 3 & 4 adverse events, serious adverse events and unexpected or events concerning to the Investigators at the time points defined above.

Stopping Guidelines / Stopping Rules

The DMEC may recommend termination or modification of the study if preliminary data indicate beyond reasonable doubt that dexamethasone confers a survival advantage. The Haybittle-Peto boundary, requiring $p<0.001$ at interim analysis to consider stopping for efficacy, should be used as a guidance. The DMEC may also recommend termination if preliminary data clearly suggest that dexamethasone is harmful in terms of survival. A less conservative $p<0.01$ in direction of harm should be used as a guidance. In addition, the DMEC will receive conditional power curves to assess whether it remains realistic that the trial will demonstrate superiority of dexamethesone conditional on the data accrued up to the point of the interim analysis. However, the DMEC recommendation should not be based purely on statistical tables and p-values but also requires clinical judgment.

Termination or modification may also be recommended for any other perceived safety concern, including but not limited to a higher than anticipated rate of treatment side effects resulting in severe adverse events or unexpected SAEs.

Adaptive Protocol Modification

There is no planned sample size re-estimation or protocol adaption; however if the DMEC reveals a need, a recommendation to re-evaluate the sample size calculation or make other changes may be put forward to the Trial Steering Committee.

Consideration of External Data

The DMEC will also consider data from other studies or external sources during its deliberations, if available, as these results may have an impact on the status of the patients and design of the current study.

DMEC Reports

Monitoring for Safety

The primary charge of the DMEC is to monitor the study for patient safety. Formal DMEC safety reviews will occur as specified above (see DMEC Meetings). The following events will also be reported to the DMEC:

- Unexpected Serious Adverse Events will be reported in detail within 2 weeks of occurrence and followed up until resolution (see appendix 1).

Safety reporting to regulatory and ethical committees will be in accordance with the requirements of each committee.

Content of DMEC Reports at Formal Interim Analyses

The detailed content of the interim analysis report will be outlined in a separate document, the Interim Analysis Plan.

Monitoring for Study Conduct

The DMEC will be updated at each scheduled meeting on study enrollment and major operational issues.

Blinding

Data will be issued to the DMEC for scheduled meetings will be unblinded. In the event of an open session, only blinded data will be presented and reviewed in the session.

DMEC Communication of Findings and Recommendations

Following each meeting and within 2 weeks of the meeting the chairman will send findings and recommendations of the DMEC in writing to the Trial Steering Committee. The report should include the date of the meeting, participants, data reviewed by the Committee and a recommendation to continue the trial with/without modification or to stop the trial on a specified basis. The report may include minutes of non-confidential relevant discussion points and any requests for clarification of further information.

These findings and recommendations can result from both the open and closed sessions of the DMEC. If these findings include serious and potentially consequential recommendations that require immediate action, the chairperson will promptly notify the Principal Investigator by phone.

Response to DMEC Findings and Recommendations

The Trial Steering Committee will review and respond to the DMEC recommendations. If the DMEC recommends continuation of the study without modification, no formal response will be required. If the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the Trial Steering Committee or Principal Investigator will provide a response stating whether the recommendations will be followed and the plan for addressing the issues.

Upon receipt, the DMEC will consider the response and will attempt to resolve relevant issues, resulting in a final decision.

The Principal Investigator will disseminate all DMEC reports, responses and final decisions to the relevant ethical committees according to the reporting requirements of that committee.

DMEC Closeout

This study may be terminated under a variety of circumstances including, but not limited to, termination for overwhelming effectiveness, futility, or safety issues per protocol or DMEC monitoring guidelines. A final study report will be issued to the DMEC who may recommend continuing action items to the Trial Steering Committee based upon the report.

Confidentiality

All data provided to the DMEC and all deliberations of the DMEC will be privileged and confidential. The DMEC will agree to use this information to accomplish the responsibilities of the DMEC and will not use it for other purposes without written consent from the Trial Steering Committee. No communication of the deliberations or recommendations of the DMEC, either written or oral, will occur except as required for the DMEC to fulfill its responsibilities. Individual DMEC members must not have direct communication regarding the study outside the DMEC (including, but not limited to the investigators, IRB/EC, regulatory agencies, or sponsor) except as authorized by the DMEC.

Amendments to the DMEC Charter

This DMEC charter can be amended as needed during the course of the study. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the report from the DMEC meetings. Each revision will be reviewed and agreed upon by both the DMEC and the Trial Steering Committee. All versions of the charter will be archived in the Trial Master File.

Archiving of DMEC Activities and Related Documents

All DMEC documentation and records will be retained in the Trial Master File in accordance with local and international regulatory requirements.

Agreement of DMEC Members

Signatures below confirm the agreement of all DMEC members to the contents of this charter and the confidentiality statement above.

Name: **Diederik van de Beek** Date: Signature:

Name: **Ronald B. Geskus** Date: Signature:

Name: **Janet Darbyshire** Date: Signature:

Name: **David Mabey** Date: Signature:

Name: **Andrew Kambugu** Date: Signature:

Agreement of Trial Steering Committee Chairman

Signatures below confirm the agreement of the TSC with the contents of this charter.

Name: Date: Signature:

UNEXPECTED SERIOUS ADVERSE EVENT (USAE) REPORT FORM

- USAEs are untoward medical events which fit one or more of the criteria for SAEs and which are not considered a part of normal clinical progression of disease or an expected drug reaction. Any event which becomes of concern to the investigators or study doctors during the course of the trial may be reported as a USAE.
- Complete one form for each USAE as soon as possible (within 7 days of USAE occurrence) with the available information. Email to Truong Tho Loc at loctt@oucru.org and Justin Beardsley at jbeardsley@oucru.org.
- If the USAE is not resolved before the first report is sent, complete all information upon resolution and resend a complete form to Truong Tho Loc at loctt@oucru.org and Justin Beardsley at jbeardsley@oucru.org.
- USAEs will be distributed to all sites for reporting to the relevant ethical committees.
- Additional pages may be added as required.
- Use this form to report any pregnancy that occurs during treatment with study dexamethasone/placebo. Upon knowledge of the pregnancy, complete the sections where information is relevant and send to the persons above. The patient should be followed until pregnancy outcome. If the child has a congenital defect or if the mother or child dies, complete the USAE form with the relevant information. If none of these apply, complete relevant details and include the statement **NOT A USAE** in section 11. Send completed forms to the persons above.

Study Code:	**04CN (CryptoDex)**	**Patient #:**	04CN -
Investigator Name:		**Patient Initials:**	
Reporter Name:		**Patient DoB:**	
Site:		**Patient Sex:**	☐ Male ☐ Female

1. EVENT:
Name of event or diagnosis: _____
_____
_____
_____

	DD	MMM	YYYY
Date of study enrolment:			
Date of event onset:			
Date when event became serious:			

2. POSSIBLE CAUSES OF THE EVENT:
(check all that apply and add lines where necessary)

Pre-existing/underlying disease – *specify all* ☐ _____
Study treatment – *specify which drug* ☐ _____
Other treatment (concomitant or previous) – *specify* ☐ _____
Protocol related procedures – *specify* ☐ _____
Other (accident, new illness, etc) – *specify* ☐ _____

3. EVENT SERIOUSNESS
Why was the event serious? (check all that apply)

Results in death ☐
Life-threatening ☐
Persistent or significant disability ☐
New in-patient hospitalization ☐
Prolonged in-patient hospitalization ☐
Congenital defect ☐

4. SAE OUTCOME

SAE outcome at the time of report:

	DD	MMM	YYYY
Fatal/Date of death ☐			
Resolved ☐			
Resolved with sequelae ☐			
Improved ☐			
Persisting ☐			
Worsened ☐			
Unknown ☐			

5. STUDY MEDICATION

Study Medication Name:	Dose:	Units:	Frequency:	Route:
Dexamethasone or Placebo		mg	Once per day	☐ IV ☐ PO

	DD	MMM	YYYY
Start Date of current dose:			
Last dose prior to SAE:			

Was the medication unblinded?

Yes ☐ No ☐

Was the drug regimen altered in response to the event? ☐ YES (specify below) ☐ No (Go to 6)

How was the drug regimen altered in response to the event?

Reduced – specify new dose ☐
Temporarily Interrupted ☐
Permanently discontinued ☐

Dates when drug regimen altered:

	DD	MMM	YYYY
Reduced			
Stopped			
Started			
Discontinued			

Details of new dose

New Dose	Units	Frequency

6. CONCOMITANT MEDICATION (include ALL current treatment but NOT drugs used to treat the SAE and NOT study medication listed above)

☐ YES (○specify below OR ○ documents attached) ☐ No

Name of drugs	Total daily dose/unit	Start Date DD / MMM / YYYY			End Date DD / MMM / YYYY			Ongoing
1.								☐
2.								☐
3.								☐
4.								☐
5.								☐
6.								☐

7. RELEVANT LABORATORY / DIAGNOSTIC TESTS (including those preceding the event)

☐ YES (○specify below OR ○ documents attached) ☐ No

Name of test	Result (Units)	Normal Values / Reference Range	Sample Collection Date			Result Pending
			DD	MMM	YYYY	
1..						☐
2.						☐

3.						☐
4.						☐

8. TREATMENT(S) / PROCEDURES FOR SAE

☐ YES (○specify below OR ○ documents attached) ☐ No

Name of treatment/procedure	Total daily dose/unit	Start Date			End Date			Ongoing
		DD	MMM	YYYY	DD	MMM	YYYY	
1.								☐
2.								☐
3.								☐
4.								☐

9. RELEVANT PREVIOUS DISEASE / MEDICAL HISTORY ☐ YES (specify below) ☐ No

Disease / Medical History	Start Date DD/MMM/YYYY			End Date DD/MMM/YYYY			Ongoing
1.							☐
2.							☐
3.							☐
4.							☐

10. RELEVANT PREVIOUS TREATMENT / PROCEDURES ☐ YES (specify below) ☐ No

Treatment History	Start Date			End Date			Ongoing
1.	DD	MMM	YYYY	DD	MMM	YYYY	☐
2.							☐
3.							☐
4.							☐

11. SAE DESCRIPTION

Detail a chronologic history of the event including: signs and characteristics, severity, dates and outcomes of hospitalization and any other relevant information not captured on this form.

……
……
……
……
……
……
……
……
……

12. Detail any additional forms or section continuations attached to this report

#	Type of Form/Attachment	Number of Pages

1.		
2.		
3.		
4.		
5.		

13. Investigator Name and Site

Investigator/Designee Signature: _____

Name: _____ **Date of Signature:** _____

Email & Telephone: _____

14. IRB and Regulatory Reporting
This USAE has been reported to the following authorities:

Authority	Reference Number	Date Sent

Section 7 Exploratory analyses of mortality

Figure: Observed difference in the absolute risk of death between dexamethasone and placebo over time (black lines), estimates+/-standard error (dark gray areas), and point-wise confidence intervals (light gray areas).

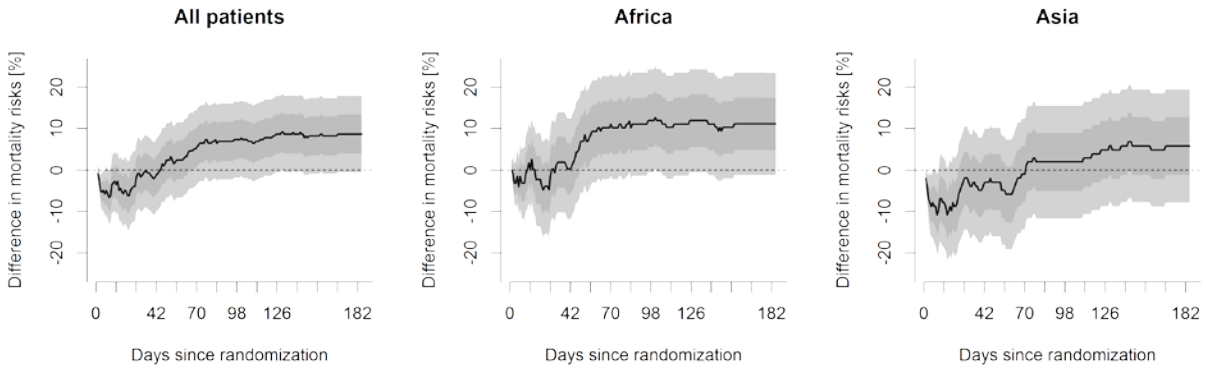

Table: Hazard ratios for mortality during days 1-22, 23-43, and 44-71. This splits the time axis into the first half of the study treatment period, the second half, and the time remaining up until 10 weeks.

Time period	**Placebo(n=226)**	**Dexamethasone(n=224)**	**Comparison**	**Test for proportional hazards**
	events/n (%)	**events/n (%)**	**HR (95%CI);p-value**	**p-value**
Days 1-22	70/226 (31)	56/224 (25)	0.77(0.54-1.09); p=0.14	0.35
Days 23-43	12/154 (8)	24/167 (14)	1.94(0.97-3.88); p=0.06	0.14
Days 44-71	11/142 (8)	26/143 (18)	2.50(1.23-5.05); p=0.01	0.94

n refers to the number of subjects at risk at the beginning of each time period.

Section 8 Definition of relapse in cryptococcal meningitis

In this trial, cryptococcal meningitis relapse was defined by one or more of:

i) the need to intensify antifungal treatment, e.g.

   a. re-introducing amphotericin,
   b. increasing the dose of fluconazole,
   c. adding a further antifungal drug to treat cryptococcal meningitis,
   d. readmission for treatment of cryptococcal meningitis

   or

ii) re-growth of C. neoformans from cerebrospinal fluid following previous sterilization

Section 9 Clinical and laboratory adverse events by type and subtype

Adverse Event	Placebo (n=226)	Dexamethasone (n=224)	Comparison (p value)
CLINICAL ADVERSE EVENTS (AE)			
Experienced any clinical AE	191 (85%)	193 (86%)	0.69
NEW NEUROLOGICAL EVENT (NNE)	59 (26%)	61 (27%)	0.83
Seizure (fit)	21 (9%)	18 (8%)	0.74
Fall in GCS >=2 points for >=48hrs	16 (7%)	17 (8%)	0.86
Headache	10 (4%)	14 (6%)	0.41
Cranial nerve palsy	11 (5%)	10 (4%)	1.00
Hemiplegia/paresis	6 (3%)	2 (1%)	0.28
Bacterial meningitis	2 (1%)	4 (2%)	0.45
Paraparesis	3 (1%)	2 (1%)	1.00
Cerebral infarction	1 (<1%)	2 (1%)	0.62
Blurred vision	1 (<1%)	2 (1%)	0.62
Altered level of consciousness	2 (1%)	1 (<1%)	1.00
Deafness (one or both ears)	0 (0%)	2 (1%)	0.25
Tetraparesis	1 (<1%)	1 (<1%)	1.00
Raised intracranial pressure	1 (<1%)	1 (<1%)	1.00
Cerebral herniation (coning)	1 (<1%)	1 (<1%)	1.00
Monoplegia/paresis	1 (<1%)	1 (<1%)	1.00
Blindness (one/both eyes)	1 (<1%)	1 (<1%)	1.00
Venous sinus thrombosis	0 (0%)	1 (<1%)	0.50
Urinary incontinence	1 (<1%)	0 (0%)	1.00
Tremors	0 (0%)	1 (<1%)	0.50
Numbness in hands	0 (0%)	1 (<1%)	0.50
Dizziness	1 (<1%)	0 (0%)	1.00
NEW AIDS DEFINING ILLNESS (NADI)	87 (38%)	87 (39%)	1.00
Progression of CM	23 (10%)	18 (8%)	0.51
Bacterial pneumonia	19 (8%)	20 (9%)	0.87
Pulmonary tuberculosis (TB)	10 (4%)	19 (8%)	0.09
Pneumonia; treated for PCP and bacterial	5 (2%)	10 (4%)	0.20
CM relapse	7 (3%)	5 (2%)	0.77
PCP	8 (4%)	3 (1%)	0.22
TB meningitis	5 (2%)	6 (3%)	0.77
Cerebral toxoplasmosis	4 (2%)	6 (3%)	0.54
Multidermatomal zoster	4 (2%)	5 (2%)	0.75
Other extrapulmonary TB	5 (2%)	3 (1%)	0.72
Kaposi''s sarcoma	5 (2%)	2 (1%)	0.45
Bacterial meningitis	0 (0%)	1 (<1%)	0.50
Cryptosporidiosis	1 (<1%)	4 (2%)	0.21

CMV end organ disease	2 (1%)	4 (2%)	0.45
Progressive multifocal leukoencephalopathy	2 (1%)	0 (0%)	0.50
Oral hairy leukoplakia	1 (<1%)	1 (<1%)	1.00
Cerebral lymphoma	0 (0%)	1 (<1%)	0.50
Salmonella septicaemia	1 (<1%)	0 (0%)	1.00
Penicilliosis	0 (0%)	1 (<1%)	0.50
Mycobacterium avium infection	0 (0%)	1 (<1%)	0.50
IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)	6 (3%)	7 (3%)	0.79
Meningitis	5 (2%)	5 (2%)	1.00
Meningitis & pneumonitis or pulmonary nodules	1 (<1%)	1 (<1%)	1.00
Other IRIS	0 (0%)	1 (<1%)	0.50
METABOLISM AND NUTRITION DISORDERS	85 (38%)	78 (35%)	0.56
Hypokalemia	75 (33%)	55 (25%)	0.05
Hyponatremia	9 (4%)	16 (7%)	0.16
Hyperglycemia	2 (1%)	13 (6%)	0.004
Hyperkalemia	2 (1%)	10 (4%)	0.02
Hypoglycemia	5 (2%)	5 (2%)	1.00
Acidosis	3 (1%)	3 (1%)	1.00
Hypoalbuminemia	1 (<1%)	2 (1%)	0.62
Electrolyte disturbance	1 (<1%)	1 (<1%)	1.00
Weight loss	0 (0%)	1 (<1%)	0.50
Hypermagnesemia	0 (0%)	1 (<1%)	0.50
BLOOD AND LYMPHATIC SYSTEM DISORDERS	83 (37%)	96 (43%)	0.21
Anemia	79 (35%)	93 (42%)	0.17
Leucocytopenia	1 (<1%)	8 (4%)	0.02
Thrombocytopenia	5 (2%)	1 (<1%)	0.22
Deep vein thrombosis	3 (1%)	1 (<1%)	0.62
Leucocytosis	0 (0%)	1 (<1%)	0.50
Coagulopathy	0 (0%)	1 (<1%)	0.50
INFECTIONS AND INFESTATIONS	25 (11%)	48 (21%)	0.003
Sepsis not specified elsewhere	17 (8%)	30 (13%)	0.05
Soft tissue infection	3 (1%)	6 (3%)	0.34
Urinary tract infection	1 (<1%)	6 (3%)	0.07
Oral herpes	2 (1%)	3 (1%)	0.68
Fever of unknown origin	0 (0%)	3 (1%)	0.12
Progression of underlying HIV	1 (<1%)	2 (1%)	0.62
Strongyloidiasis	1 (<1%)	1 (<1%)	1.00
Genital herpes	1 (<1%)	1 (<1%)	1.00
Perianal abscess	0 (0%)	1 (<1%)	0.50

Acute febrile illness	0 (0%)	1 (<1%)	0.50
Malaria	1 (<1%)	0 (0%)	1.00
Lung abscess	1 (<1%)	0 (0%)	1.00
Liver abscess	1 (<1%)	0 (0%)	1.00
GASTROINTESTINAL (GI) DISORDERS	16 (7%)	29 (13%)	0.04
Diarrhoea	7 (3%)	19 (8%)	0.02
Upper GI bleeding	3 (1%)	4 (2%)	0.72
Vomiting	3 (1%)	2 (1%)	1.00
Gastroenteritis unspecified	1 (<1%)	2 (1%)	0.62
Rectal prolapse	1 (<1%)	0 (0%)	1.00
Perforated appendicitis	0 (0%)	1 (<1%)	0.50
Peptic ulcer	0 (0%)	1 (<1%)	0.50
Partial intestinal obstruction	0 (0%)	1 (<1%)	0.50
Gastric ulcer	0 (0%)	1 (<1%)	0.50
Abdominal pain	0 (0%)	1 (<1%)	0.50
Lower GI bleeding	1 (<1%)	0 (0%)	1.00
RENAL AND URINARY DISORDERS	7 (3%)	22 (10%)	0.004
Acute renal failure	7 (3%)	19 (8%)	0.02
Acute urinary retention	0 (0%)	1 (<1%)	0.50
Haemolytic uremic syndrome	0 (0%)	1 (<1%)	0.50
Haematuria	0 (0%)	1 (<1%)	0.50
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14 (6%)	9 (4%)	0.39
Pneumonitis	8 (4%)	5 (2%)	0.58
Aspiration	2 (1%)	1 (<1%)	1.00
Pleural effusion	2 (1%)	0 (0%)	0.50
Hypoxia	0 (0%)	1 (<1%)	0.50
ARDS	1 (<1%)	0 (0%)	1.00
Respiratory failure	0 (0%)	1 (<1%)	0.50
Pleuritis	1 (<1%)	0 (0%)	1.00
Apnea	0 (0%)	1 (<1%)	0.50
Dyspnea	0 (0%)	1 (<1%)	0.50
HEPATOBILIARY DISORDERS	3 (1%)	10 (4%)	0.05
Jaundice	3 (1%)	5 (2%)	0.50
Hepatitis	2 (1%)	5 (2%)	0.28
VASCULAR DISORDERS	4 (2%)	9 (4%)	0.17
Hypertension	1 (<1%)	8 (4%)	0.02
Hypotension	3 (1%)	1 (<1%)	0.62
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (1%)	6 (3%)	0.34
Hyperpigmentation	1 (<1%)	2 (1%)	0.62
Pressure sore	2 (1%)	1 (<1%)	1.00
Apthous ulcers	0 (0%)	2 (1%)	0.25
Subcutaneous emphysema	0 (0%)	1 (<1%)	0.50

CARDIAC DISORDERS	0 (0%)	8 (4%)	0.004
Arrhythmia	0 (0%)	5 (2%)	0.03
Congestive heart failure	0 (0%)	3 (1%)	0.12
ENDOCRINE DISORDERS	3 (1%)	3 (1%)	1.00
Hypoadrenalism	3 (1%)	3 (1%)	1.00
PSYCHIATRIC DISORDERS	1 (<1%)	3 (1%)	0.37
Confusion	1 (<1%)	1 (<1%)	1.00
Psychiatric illness	0 (0%)	2 (1%)	0.25
IMMUNE SYSTEM DISORDERS	1 (<1%)	1 (<1%)	1.00
Stevens-Johnson syndrome	1 (<1%)	1 (<1%)	1.00
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (<1%)	2 (1%)	0.62
Allergic reaction	1 (<1%)	2 (1%)	0.62
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0%)	1 (<1%)	0.50
Breast mass	0 (0%)	1 (<1%)	0.50
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (<1%)	0 (0%)	1.00
Abortion	1 (<1%)	0 (0%)	1.00
SYSTEMIC	1 (<1%)	0 (0%)	1.00
Multi organ failure	1 (<1%)	0 (0%)	1.00
LABORATORY AEs			
Experienced any lab AE	192 (85%)	202 (90%)	0.12
Anaemia	112 (50%)	120 (54%)	0.4
Leukocytopenia	41 (18%)	36 (16%)	0.62
Neutropenia	59 (26%)	42 (19%)	0.07
Thrombocytopenia	25 (11%)	33 (15%)	0.26
Elevated ALT	3 (1%)	10 (4%)	0.05
Elevated AST	11 (5%)	14 (6%)	0.54
Hyperglycemia	6 (3%)	32 (14%)	<0.001
Hypoglycemia	6 (3%)	5 (2%)	1.00
Hypercreatinemia	50 (22%)	79 (35%)	0.002

Section 10 Summary of all pre-specified subgroup analyses for mortality by 10 weeks and 6 months

*Subgroup	Placebo (n=226)	Dexamethasone (n=224)	Comparison Estimate (95% CI); p-value	**Test for heterogeneity
Deaths by week 10				
ITT	93/226 (41%)	106/224 (47%)	1.11(0.84-1.47); p=0.45	
Per Protocol	87/213 (41%)	103/213 (49%)	1.16(0.87-1.54); p=0.31	
Continent				0.32
Africa	51/124 (42%)	63/122 (52%)	1.26(0.87-1.82); p=0.23	
Asia	42/102 (41%)	43/102 (42%)	0.95(0.62-1.45); p=0.80	
GCS				0.16
-15	60/176 (34%)	82/187 (44%)	1.29(0.93-1.80); p=0.13	
- <15	33/50 (66%)	23/36 (64%)	0.86(0.51-1.48); p=0.60	
ART status				0.35
- ART naïve	57/133 (43%)	68/135 (50%)	1.15(0.81-1.63); p=0.45	
- On ART <=3 months	16/46 (35%)	21/41 (51%)	1.49(0.77-2.87); p=0.23	
- ART for >3 months	20/47 (43%)	17/48 (36%)	0.77(0.40-1.47); p=0.43	
Gender				0.85
- Female	39/94 (42%)	37/77 (48%)	1.15(0.73-1.80); p=0.55	
- Male	54/132 (41%)	69/147 (47%)	1.09(0.76-1.55); p=0.65	
Age				0.09
- <=35 years	35/118 (30%)	48/117 (41%)	1.47(0.95-2.28); p=0.08	
- >35 years	58/108 (54%)	58/107 (55%)	0.89(0.62-1.28); p=0.54	
CSF quantitative fungal count				0.43
- $<10^5$ CFU/ml	47/131 (36%)	63/141 (45%)	1.24(0.85-1.81); p=0.26	
- $>10^5$ CFU/ml	42/81 (53%)	35/63 (56%)	0.99(0.63-1.56); p=0.98	
Baseline CD4 count				0.40
- <=25 cells/µL	49/117 (43%)	62/122 (51%)	1.24(0.85-1.80); p=0.27	
- >25 cells/µL	39/97 (40%)	38/90 (42%)	0.96(0.61-1.50); p=0.86	
Baseline opening pressure				0.67
- <=18 cmCSF	29/68 (43%)	32/71 (45%)	1.00(0.60-1.66); p=1.00	
- >18 cmCSF	57/135 (43%)	64/129 (50%)	1.14(0.80-1.63); p=0.47	
Baseline CSF white cell count				0.11
- <5 cells/µl	12/17 (71%)	11/25 (44%)	0.53(0.23-1.21); p=0.13	
- >=5 cells/µl	79/195 (41%)	90/188 (48%)	1.13(0.83-1.53); p=0.43	
Deaths by month 6				
ITT	109/226 (49%)	128/224 (57%)	1.18(0.91-1.53); p=0.20	
Per Protocol	103/213 (48%)	125/213 (59%)	1.23(0.95-1.60); p=0.12	
Continent				0.50
Africa	62/124 (51%)	75/122 (62%)	1.28(0.91-1.79); p=0.16	
Asia	47/102 (46%)	53/102 (52%)	1.06(0.72-1.58); p=0.76	
GCS				0.13

-15	73/176 (42%)	101/187 (54%)	1.36(1.00-1.83); p=0.05	
- <15	36/50 (72%)	26/36 (72%)	0.88(0.53-1.46); p=0.62	
ART status				0.29
- ART naïve	65/133 (49%)	83/135 (61%)	1.27(0.92-1.76); p=0.15	
- On ART <=3 months	21/46 (47%)	25/41 (61%)	1.41(0.79-2.53); p=0.24	
- ART for >3 months	23/47 (50%)	20/48 (42%)	0.79(0.43-1.44); p=0.44	
Gender				0.97
- Female	47/94 (51%)	45/77 (59%)	1.18(0.79-1.78); p=0.42	
- Male	62/132 (47%)	83/147 (56%)	1.18(0.85-1.64); p=0.33	
Age				0.13
- <=35 years	46/118 (40%)	61/117 (52%)	1.48(1.01-2.18); p=0.04	
- >35 years	63/108 (58%)	67/107 (63%)	0.97(0.69-1.37); p=0.85	
CSF quantitative fungal count				0.42
- $<10^5$ CFU/ml	57/131 (44%)	76/141 (54%)	1.28(0.91-1.81); p=0.15	
- $>10^5$ CFU/ml	46/81 (58%)	39/63 (62%)	1.02(0.67-1.57); p=0.91	
Baseline CD4 count				0.80
- <=25 cells/µL	61/117 (53%)	74/122 (61%)	1.23(0.87-1.73); p=0.24	
- >25 cells/µL	40/97 (41%)	45/90 (50%)	1.12(0.73-1.72); p=0.60	
Baseline opening pressure				0.68
- <=18 cmCSF	35/68 (51%)	41/71 (58%)	1.10(0.70-1.74); p=0.68	
- >18 cmCSF	63/135 (47%)	75/129 (58%)	1.23(0.88-1.72); p=0.22	
Baseline CSF white cell count				0.07
- <5 cells/µL	12/17 (71%)	12/25 (48%)	0.57(0.25-1.28); p=0.17	
- >=5 cells/µL	92/195 (47%)	111/188 (59%)	1.24(0.94-1.64); p=0.12	

ITT (intention to treat), GCS (Glasgow Coma Score), ART (anti-retroviral therapy), CSF (cerebrospinal fluid)

*At study entry. In addition to probable unmasking IRIS (which is covered by the subgroup analysis by ART status), subgroup analyses by other IDSA indications for steroid treatment at baseline were also pre-defined. However, numbers were too low (no patients with cryptococcoma with mass effect and only three patients with acute respiratory distress syndrome) to actually perform the respective subgroup analyses.

** Heterogeneity was assessed with likelihood ratio tests for an interaction between treatment assignment and the grouping variable