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1. Trial Objectives and Endpoints

1.1. Trial Objectives

This is an extension study of the IBM4809 study, which recently reported results, and showed that the treatment was not effective in treating IBM. It would have been unethical to continue with the OLE study, as patients would not be expected to benefit from it.

Following the early termination of the study by the Sponsor, this statistical analysis plan (SAP) is focused on safety analysis. All assessments supposed to be used in the efficacy part will be summarized in tables by using descriptive statistics and presented in the listing, but no specific efficacy analysis will be performed.

Consequently, this SAP is designed to outline the methods to be used in the analysis of study data to answer the safety objectives.

1.1.1. Primary Objectives

Before termination of study the primary objective was to determine the efficacy (based on the Inclusion Body Myositis Functional Rating Scale [IBMFRS]) of early* versus delayed start of arimoclomol treatment of IBM up to Month 20 in the OLE trial.

1.1.2. Secondary Objectives

Before termination of study the secondary objectives were to determine the efficacy (on secondary efficacy endpoints) of early* versus delayed start of arimoclomol treatment of IBM up to Month 20 and up to Month 40 in the OLE trial. Another secondary objective was to determine the safety and tolerability of long-term treatment of IBM with arimoclomol up to Month 40 in the OLE trial.

1.1.3. Exploratory Objectives

Before termination of study the exploratory objectives were [redacted] to explore population pharmacokinetics (popPK) and popPK/PD and to determine the efficacy (on secondary efficacy endpoints) of early** versus delayed start of arimoclomol treatment over periods of 20 months duration.

* Including 20 months arimoclomol treatment and 20 months placebo treatment from trial IBM4809 for the early and delayed start group, respectively.

** Including (only) 20 months arimoclomol treatment from trial IBM4809 for the early start group

1.2. Trial Endpoints

1.2.1. Efficacy Endpoints

Due to early termination of study by Sponsor the efficacy endpoints were revised, and most of them will not be analysed, since the focus were moved to the safety evaluations.

1.2.1.1. Primary and Secondary Efficacy Endpoint

Before termination of study the primary efficacy endpoint of this trial was change in the IBMFRS total score from IBM4809 baseline to Month 20 in the OLE trial.

Before termination of study by Sponsor the secondary efficacy endpoints were change in 6-Minute Walk Test Distance, change in Modified Timed Up and Go (mTUG), change in MVICT of the quadriceps muscle, change in hand grip strength, change in SF-36 from IBM4809 baseline to Month 20 in the OLE trial, change in the IBMFRS total score from IBM4809 baseline to Month 40 in the OLE trial, and change in hand grip strength from IBM4809 baseline to Month 40 in the OLE trial, and number of Falls and Near Falls from IBM4809 baseline to Month 20 in the OLE trial.

1.2.2. Safety Endpoints

The safety endpoints will be on the main focus of this trial and will include the following (to 40 months):

- Adverse events (AEs), SAEs
- Clinical safety laboratory tests
- Vital signs
- ECGs
- Columbia Suicide Severity Rating Scale (C-SSRS)

1.2.3. Exploratory Endpoints

Due to early termination of study by Sponsor the exploratory endpoints will not be analysed.

Before termination of study the exploratory endpoints included the following: population pharmacokinetics (popPK) and popPK/PD, change from baseline* over 20 months of arimoclomol treatment in IBMFRS total score, 6-Minute Walk Test Distance, Modified Timed Up and Go (mTUG), MVICT of the quadriceps muscle, hand grip strength, and SF-36 in arimoclomol naïve patients

* Baseline is defined at the visit at which the subject receives first administration of arimoclomol (corresponding to IBM4809 baseline and IBMOLE baseline for patients randomized to arimoclomol and placebo in IBM4809, respectively)

1.2.4. Pharmacokinetic/Pharmacodynamic Variable(s)

Due to early termination of study by Sponsor the PK/PD endpoints will not be analysed.

Before termination of study the pharmacokinetic (PK) endpoints of the trial were to constitute arimoclomol plasma concentrations The calculation of parameters for population PK analysis was planned to be described in a separate PK analysis plan (PKAP), but won`t be performed.

2. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Orphazyme A/S protocol number IBM-OLE (An open-label, non-randomized trial to investigate the efficacy and safety of early versus delayed start of arimoclomol in patients with sporadic inclusion body myositis who have completed the IBM4809 trial) and any updates hereof. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (1). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (2) and the Royal Statistical Society (3), for statistical practice.

The planned analyses identified in this SAP may be included in clinical trial reports (CTRs), regulatory submissions, or future manuscripts.

Since the study was terminated by the Sponsor, study objectives and endpoints were revised, hence the actual analysis will differ from what was defined in the Study Protocol. In case of differences between SAP and protocol, this SAP takes precedence.

Also, post-hoc exploratory analyses, not necessarily identified in this SAP, may be performed to further examine trial data. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such in the final CTR.

The statistical plan described hereafter is an *a priori* plan. It will be finalized and approved prior to database lock (DBL), i.e. prior to descriptive analysis of the data pertaining to the IBM-OLE trial.

3. Overall Trial Design and Plan

3.1. Overall Design

This Phase 3b, multicenter, nonrandomized, open-label, uncontrolled clinical extension trial is designed to compare the efficacy and safety of early versus delayed start of arimoclomol in the treatment of IBM.

Up to 150 male and female patients who have completed the IBM4809 trial will be available for this trial. Patients must currently be on treatment with the investigational medicinal product (IMP) from the blinded IBM4809 trial (arimoclomol or placebo) and will enroll in this trial at Visit 14/Month 20 of the blinded IBM4809 trial. In this trial there will be two treatment groups:

- Early group (patients who received arimoclomol in the blinded IBM4809 trial)
- Delayed group (patients who received placebo in the blinded IBM4809 trial)

11 trial sites in the United States and 1 trial site in the United Kingdom.

Patients who completed the IBM4809 study at a reduced dose of 600 mg/day arimoclomol citrate (200 mg t.i.d.) will continue to receive their reduced dose in this open-label extension (OLE) study. All other patients will receive 1200 mg/day arimoclomol citrate (400 mg t.i.d.).

The duration of treatment in this trial was supposed to be 40 months, but the study was early terminated by the Sponsor.

The trial was expected to be split into two treatment periods with remaining the same throughout the two treatment periods.

Treatment period 1:

Patients will be seen in the clinic at baseline and months 1, 5 and 9, 15 and 20. Visits will be conducted by telephone at month 2, 3, 4, 6, 12 and 18. For the telephone visits at month 2, 3, 4 and 6 a clinical safety laboratory assessment is also required.

Efficacy part will be revised and assessed by the descriptive summary of IBMFRS total score, 6-Minute Walk Test, Modified Timed Up and Go (mTUG), Maximal Voluntary Isometric Contraction Testing (MVICT) of the quadriceps muscle, hand grip strength testing, 36-Item Short Form Health Survey (SF-36), and falls and near falls.

[redacted] Sparse PK samples were supposed to be collected for popPK analysis and explorative popPK/PD modeling (reported separately). Additional blood was expected to be drawn for biobanking for future potential tests. But due to early termination of study, [redacted] PK/PD analysis won`t be performed.

Safety will be assessed by evaluating adverse events (AEs), clinical safety laboratory test results, vital sign measurements, 12-lead electrocardiograms (ECGs), and the Columbia Suicide Severity Rating Scale (C-SSRS).

Treatment period 2:

Patients supposed to be seen in the clinic at months 23, 29, 35 and 40. Visits supposed to be conducted by telephone at month 26, 32 and 38.

Efficacy were planned to be assessed by the in-clinic IBMFRS total score and hand grip strength testing. Safety will be assessed by evaluating AEs, clinical laboratory test results and C-SSRS. All AEs observed by the trial personnel or reported by the patient during the trial (from the time of visit 1(screening) in IBM-OLE) will be collected.

If a patient discontinues treatment (or the trial is terminated) an early termination (ET) visit will be performed as soon as possible after discontinuation, with a follow-up ET phone assessment 2 weeks later. Depending on the timing of discontinuation (before or after Month 20) the assessments performed at the ET visit differs according to the relevant visit schedule (Treatment period 1 and Treatment period 2).

[redacted]

3.2. Sample Size and Power

As this trial is an open-label extension planning to include patients from the previous trial (IBM4809), no calculation for sample size was performed.

3.3. Trial Population

Patients with sporadic IBM according to the protocol/meeting the eligibility criteria, who have completed the IBM4809 trial.

3.4. Treatments Administered and Method of Assigning Patients to Treatment Groups

In this open-label, single-treatment trial, all patients will receive the same treatment (arimoclomol citrate).

Patients who completed the IBM4809 study at a reduced dose of 600 mg/day arimoclomol citrate or reduced placebo dose will continue on reduced dose arimoclomol citrate in this OLE study. All other patients in this open-label extension trial will be assigned to receive 1200 mg/day arimoclomol citrate (400 mg t.i.d.).

3.5. Blinding and Unblinding

During the OLE trial, patients must remain blinded as to their treatment assignment in IBM4809.

3.6. Schedule of Events

A detailed schedule of events planned for the trial is provided in Table 1 (Treatment period 1) and Table 2 (Treatment period 2) below.

Table 1: Schedule of Events - Treatment period 1 (Month 0-20)

Visit #	1	2	3 (phone visit)	4 (phone visit)	5 (phone visit)	5a	6 (phone visit)	7	8 (phone visit)	9	10 (phone visit)	11/ ET[a]
Month	**0[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**20**
Consent	X											
Eligibility	X											
Demographics	X											
Medical History	X[b]											
Vital signs, including weight	X[b]	X				X		X		X		X
Physical Examination	X[b]	X				X		X		X		X
Electrocardiogram	X[b]							X				X
Clinical Safety Lab Tests	X	X	X	X	X	X	X	X		X		X
Urine Pregnancy Test	X[b]	X				X		X		X		X
Dispensing of Medication	X	X				X		X		X		X
First dose of open-label arimoclomol	X											
Return of Medication		X				X		X		X		X
C-SSRS	X[b]	X	X	X	X	X	X	X	X	X	X	X
MVICT of the quadriceps muscle	X[b]							X				X
SF-36	X[b]							X				X
Falls diary	X[b]	X				X		X		X		X
Hand Grip Strength	X[b]							X				X
IBMFRS	X[b]	X				X		X		X		X
6MWT	X[b]					X		X		X		X
mTUG	X[b]					X		X		X		X
[redacted]	[redacted]								[redacted]			[redacted]
Biobank Samples	X[b]							X				X
PopPK Samples								X				X
Concomitant Medication	X[b,d]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[b,d]	X	X	X	X	X	X	X	X	X	X	X

Table 2: Schedule of Events – Treatment period 2 (Month 21-40)

Visit #	12	13 (phone visit)	14	15 (phone visit)	16	17 (phone visit)	18/ ET[f]	19 (Safety follow up)
Month	**23**	**26**	**29**	**32**	**35**	**38**	**40**	**ET +2 wks**
Vital signs, including weight	X		X		X		X	
Clinical Safety Lab Tests	X		X		X		X	
Urine Pregnancy Test	X		X		X		X	
Dispensing of Medication	X	X	X	X	X	X		
Return of Medication	X		X		X		X	
C-SSRS	X	X	X	X	X	X	X	
IBMFRS	X		X		X		X	
Hand Grip Strength	X		X		X		X	
Concomitant Medication	X	X	X	X	X	X	X	X[e]
Adverse Events	X	X	X	X	X	X	X	X[e]

Phone visits are shaded gray.

Abbreviations: 6MWT = 6-Minute Walk Test; C-SSRS = Columbia Suicide Severity Rating Scale; ET = early termination; IBMFRS = Inclusion Body Myositis Functional Rating Scale; [redacted]; mTUG = Modified Timed Up and Go; MVICT = Maximal Voluntary Isometric Contraction Testing; PopPK = population pharmacokinetics; SF-36 = 36-Item Short Form Health Survey.

Note: Visit windows for all visits are ± 7 days relative to Visit 1.

a. If a patient discontinues during treatment period 1 (or the trial is terminated) before Visit 11/Month 20, an ET visit for treatment period 1 (month 20) will be performed as soon as possible after discontinuation, with a safety follow up phone visit 2 weeks later.
b. Data from the completion visit of IBM4809 will be transferred to Visit 1 of IBM-OLE if required in the OLE trial, but not collected, except for safety labs, which require samples for both studies.
c. [redacted]
d. Ongoing AEs and concomitant medications from IBM4809 should be recorded in the IBM-OLE eCRF.
e. Assess and record SAEs occurring since the last evaluation and collect stop dates for already ongoing AEs.
f. If a patient discontinues during treatment period 2 (or the trial is terminated) between Visit 11/Month 20 and Visit 18/Month 40, an ET visit for treatment period 2 (month 40) will be performed as soon as possible after discontinuation, with a safety follow up phone visit 2 weeks later.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation (SD), median, minimum, maximum, quartile 1 and quartile 3.

Categorical (qualitative) variable summaries will include the number of patients (n) with non-missing values, frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of patients in the relevant analysis population for the treatment groups, unless otherwise specified. The denominator for by-visit displays will be the number of patients in the relevant analysis population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and standard deviation (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Section 6.2 describes rules for deciding which visits/assessments are eligible for which analysis. Please note that all data will appear in lists and for analysis non-eligible data points will be highlighted in the lists.

5. Analysis Populations & Treatment Durations

5.1. Analysis Populations

The following analysis populations are planned for this trial:

- **Safety Population:** All patients who receive at least 1 dose or partial dose of arimoclomol in the extension trial. Safety analyses will be performed on the Safety Population.
- **Modified Intent-to-treat (mITT) Population:** All patients receiving at least 1 dose or partial dose of arimoclomol in the extension trial, with a baseline value and at least 1 post-baseline value for IBMFRS. Efficacy analyses will be performed on the mITT Population.

Inclusion in the analysis populations will be determined prior to database lock

5.2. Observation Period

Patients and data to be used in an analysis will be selected in a two-step manner.

- Firstly, patients will be selected based on the specified analysis set (mITT, SAF or All screened patients)
- Secondly, data points from the selected patients from the first step will be selected.

Since the study was terminated by the Sponsor, exploratory endpoints, that include comparison with the baseline of main IBM4809 study, will not be analysed.

All by-visit statistics will summarize the data at each scheduled visit and change from OLE baseline.

Baseline will be the assessment performed at the month 0 of this OLE study, if applicable.
If not applicable, then the baseline will be the last assessment transferred from the main Visit 14/Month 20 of IBM4809 study.

Only scheduled visits will be tabulated, with exception of including unscheduled visits to outlier tables (laboratory abnormality etc.). All visits (scheduled and unscheduled) will be included in the listings.

Medical history data (from OLE study as well as transferred from IBM4809) will be listed and tabulated.

Adverse events that start or continue inside the OLE timeline only will be summarized and listed (the overview table will summarize both AEs and TEAEs, but the subsequent tables will be performed for TEAEs only). AEs that started and finished before 1st dose in the OLE study won`t be presented.
Medications starting or continuing beyond the first dose in OLE study will be considered as concomitant regardless they were before the last dose of IMP or after. Medications started and finished before 1st dose in the OLE will be treated as prior.

6. Statistical Analysis

6.1. Baseline

In this open-label extension trial baseline will be the last observation recorded prior to the first dose in the OLE study.

Baseline will be the assessment performed at the month 0 of this OLE study, if applicable. If not applicable, then the baseline will be the last assessment transferred from the main Visit 14/Month 20 of IBM4809 study.

Patients must currently be on treatment with the IMP from the blinded IBM4809 trial (arimoclomol or placebo), and some assessments performed at Visit 14/Month 20 of the blinded IBM4809 trial will serve as a baseline, while others will be collected at baseline of this OLE study.

The following procedures performed at Visit 14/Month 20 of the blinded IBM4809 trial will serve as the baseline evaluations for this trial:
1. Measure vital signs, including weight.
2. Perform a physical examination.
3. Perform a 12-lead ECG.
4. Perform a urine pregnancy test for female patients of childbearing potential.
5. Record concomitant medications and concomitant therapies.
6. Assess and record AEs occurring since the last evaluation.
7. Complete the IBMFRS, MVICT of quadriceps muscle, mTUG, hand grip strength testing, 6-minute walk test, and SF-36.
8. Complete the C-SSRS ("since last visit" assessment).
9. Collect and review the falls diary.

(NOTE: If this extension trial has not yet been initiated at a patient's clinical site or if the patient are not able to perform in-clinic visits due to COVID-19 when the patient completes Visit 14, that patient may enroll in this trial up to 12 weeks after Visit 14/Month 20 of the blinded IBM4809 trial. Such patients will need to undergo the full set of baseline assessments, and the investigator must confirm eligibility. This possibility will only be available if the patient is able to perform visit 14 in the IBM4809 trial before 01-Feb-2021).

The following procedures will be performed at baseline for this OLE trial:
1. Obtain written informed consent (and/or assent if applicable).
2. Record demographics.
3. Record medical history.
4. Assess inclusion/exclusion criteria.
5. Collect blood for safety laboratory tests and biobanking.
6. When all baseline procedures are completed and the site investigator confirms that the patient is eligible, enroll the patient.
7. Administer the first dose of open-label arimoclomol and observe for 1 hour after dosing.
8. Dispense arimoclomol for the initial 1-month period and give the patient instructions regarding dosing schedule and trial requirements.
9. Give the patient a new falls diary

6.2. Analysis Visit Windows

The summary and analysis of the trial endpoints by visit is conditioned on each patient contributing no more than one observation per visit. As some parameters may have assessments occurring very close in time and thus may be attributable to the same planned visit, an algorithm whereby maximally 1 (one) is being selected for summary analysis is detailed below:

Visit windows vary depending on the specific assessment. The visit windows for each assessment are shown in Table 3 to Table 8 below.

In the presented tables, the rule for calculating the nominal day (ADY) for a given visit *I* with a given nominal month m_i is given as ADY=30· m_i +1. Also as a general rule, the upper bound for a visit is the mean of the nominal day of the given visit and the nominal day the next visit $i+1$ ($15\cdot(m + m_{i+1})$). The lower bound is the upper bound of the preceding visit + 1. As an exception from the general rule, windows are restricted by the exception that a window for a given parameter cannot exceed +/- 60 days (2 months) and can also not extend beyond the nominal time of a neighbouring visit, at which the given parameter is scheduled to be collected

Scheduled assessments will be assigned to the visit at which they are scheduled. If they are outside the acceptable windows shown in the tables below, they will be flagged such that they are not used in summary statistics.

Unscheduled visits will be mapped to the appropriate visit depending on which visit window they fall within.

The final in-person visit is normally scheduled for month 40, but may be done earlier for early dropouts. In those cases, the observations at the final in-person visit are also mapped to the appropriate visit based on the visit window. If unscheduled visits or the final in-person visit do not fall within any visit window, they will be left described as "unscheduled".

If there is more than one observation per assessment within the same visit window, then the observation with the closest day to the nominal day will be selected for analysis and any other observations will be disregarded. If 2 observations have the same distance from the nominal day, then a scheduled visit will be preferred to an unscheduled visit, and if both observations are of the same type, then the earlier visit will be preferred.

Table 3: Window bounds for scheduled IBMFRS , Vital signs assessments and Urine Pregnancy Test (visits 1, 2, 5a, 7, 9, 11, 12, 14, 16 and 18)

Visit	Month	Nominal time (Analysis Relative Day)	Lower bound (Analysis Relative Day)	Upper bound (Analysis Relative Day)
V1	0	1	NA	1
V2	1	31	2	91
V5a	5	151	92	211
V7	9	271	212	331
V9	15	451	392	511

V11	20	601	541	646
V12	23	691	647	751
V14	29	871	812	931
V16	35	1051	992	1111
V18	40	1201	1142	1261

Table 4: Window bounds for ECG and SF-36 scheduled assessments (visits 1, 7 and 11)

Visit	Month	Nominal time (Analysis Relative Day)	Lower bound (Analysis Relative Day)	Upper bound (Analysis Relative Day)
V1	0	1	NA	1
V7	9	271	211	331
V11	20	601	541	661

Table 5: Window bounds for Hand Grip Strength scheduled assessments (visits 1, 7, 11, 12, 14, 16 and 18)

Visit	Month	Nominal time (Analysis Relative Day)	Lower bound (Analysis Relative Day)	Upper bound (Analysis Relative Day)
V1	0	1	NA	1
V7	9	271	211	331
V11	20	601	541	646
V12	23	691	647	751
V14	29	871	811	931
V16	35	1051	991	1111
V18	40	1201	1141	1261

Table 6: Window bounds for 6MWD and MTUG scheduled assessments pattern at (visits 1, 5a, 7, 9 and 11

Visit	Month	Nominal time (Analysis Relative Day)	Lower bound (Analysis Relative Day)	Upper bound (Analysis Relative Day)
V1	0	1	NA	1
V5a	5	151	91	211
V7	9	271	212	331
V9	15	451	391	511
V11	20	601	541	661

Table 7: Window bounds for C-SSRS scheduled assessments visits (1, 2, 3, 4, 5, 5a, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18)

Visit	Month	Nominal time (Analysis Relative Day)	Lower bound (Analysis Relative Day)	Upper bound (Analysis Relative Day)
V1	0	1	NA	1
V2	1	31	2	46
V3	2	61	47	76
V4	3	91	77	106
V5	4	121	107	136
V5a	5	151	137	166
V6	6	181	167	226
V7	9	271	227	316
V8	12	361	317	406
V9	15	451	407	496
V10	18	541	497	571
V11	20	601	572	646
V12	23	691	647	736
V13	26	781	737	826
V14	29	871	827	916
V15	32	961	917	1006
V16	35	1051	1007	1126
V18	40	1201	1141	1261

Table 8: Window bounds for Lab scheduled assessments visits (1, 2, 3, 4, 5, 5a, 6, 7, 9, 11, 12, 14, 16 and 18)

Visit	Month	Nominal time (Analysis Relative Day)	Lower bound (Analysis Relative Day)	Upper bound (Analysis Relative Day)
V1	0	1	NA	1
V2	1	31	2	46
V3	2	61	47	76
V4	3	91	77	106
V5	4	121	107	136
V5a	5	151	137	166
V6	6	181	167	226
V7	9	271	227	331
V9	15	451	392	511

V11	20	601	542	646
V12	23	691	647	751
V14	29	871	811	931
V16	35	1051	992	1111
V18	40	1201	1141	1261

6.3. Multiple Comparisons

Not applicable for this OLE study. No efficacy testing will be performed.

6.4. Efficacy Endpoints

Since the study was terminated by Sponsor, the efficacy analysis was simplified from what was planned in the Study Protocol: no hypothesis testing for the effectiveness between the early-start group and delayed-group will be performed.

6.4.1. Analyses of Primary Endpoint

The descriptive statistics for IBMFRS total score at each visit and change from baseline will be presented: the number of non-missing values at each visit, mean, median, standard deviation, minimum, maximum, 1st, and 3rd quartiles will be tabulated. No summarization will be performed for sub-domains.

The baseline value for the IBMFRS assessment will be copied from the completion visit of IBM4809 and will be transferred to this OLE study.

All IBMFRS data will be presented in listing.

Missing data will not be imputed.

6.5. Analyses of Secondary Endpoints

Since the study was terminated by Sponsor, the efficacy analysis was simplified from what was planned in the Study Protocol: no hypothesis testing for the effectiveness in secondary endpoints between the early-start group and delayed-group will be performed.

Missing data will not be imputed.

6.5.1. Six Minutes Walking distance test; distance at 6 minutes (6MWD)

The descriptive statistics for 6 Minute Walk Test Distance at each visit and change from baseline will be summarized using descriptive statistics.

The OLE baseline value for the 6 Minute Walk Test assessment will be the assessment transferred from the completion visit of IBM4809.

All 6MWD data will be presented in listing.

6.5.2. Modified Timed Up and Go (mTUG)

When summarizing the Modified Timed Up and Go, the reciprocal of the measured time will be used, multiplied by the planned total distance of 6 meter. This corresponds to analysing the velocity of the walking speed expressed in meters per seconds (m/s), including the time spent for standing up and sitting down again.

The descriptive statistics for Modified Timed Up and Go Test at each visit and change from baseline will be presented: the number of non-missing values at each visit, mean, median, standard deviation, minimum, maximum, 1st, and 3rd quartiles will be tabulated

The OLE baseline value for the Modified Timed Up and Go Test assessment will be the assessment transferred from the completion visit of IBM4809.

All mTUG data will be presented in the listing.

6.5.3. Grip strength using the Jamar device

Grip strength is assessed for both the right and the left hand.

The result used in the confirmatory analysis will be the result for the strongest hand, which is determined at baseline. The right hand will be deemed the strongest if it has a value equal to or higher than the left side (at baseline). If both values are missing, the right hand will be assumed the strongest.

During the conduct of the trial, a concern for potential inaccuracy of reporting of units used for hand grip strength measurements was raised. To mitigate this concern, a question was retrospectively added to the relevant CRF, asking whether the site could confirm that the hand grip strength results were entered in kg units. The question had thereby the characteristics of a data query implemented via the eCRF (EDC).

In a number of such records, the site answered that they could not confirm the unit used (i.e. they did also not reject the originally reported unit). It will be assumed that the correct unit has been reported for these records.

The number of non-missing values at each visit as well as change from the baseline will be tabulated using mean, median, standard deviation, minimum, maximum, 1st, and 3rd quartiles.

All hand grip results will be listed.

6.5.4. Quadriceps Muscle Strength Testing

Maximal voluntary isometric contraction testing (MVICT) of the patient's quadriceps muscle will be performed using the MicroFET hand myometer. This is a hand-held device that allows the examiner to push against a muscle while the patient resists. The patient will be encouraged by the clinical evaluator (CE) to exert maximal effort. Each test will be performed twice on each side and both sets of results will be recorded.

The descriptive statistics for MVICT at each visit and change from baseline will be presented: the number of non-missing values at each visit, mean, median, standard deviation, minimum, maximum, 1st, and 3rd quartiles will be tabulated

The OLE baseline value for the MVICT assessment will be the assessment transferred from the completion visit of IBM4809.

All MVICT results will be listed.

6.5.5. Falls and Near Falls

All falls and near falls data will be listed, no tabulation will be done.

6.5.6. SF-36 Results

The raw values of the SF-36 results will be presented in the listing. No derived scores will be calculated.

6.6. Derived Variables

Entity	Definition
Change from baseline	Value at current timepoint – value at baseline
BMI	Weight in kilograms / (Height in meters) ^2
Treatment day	assessment date – date of first dose + 1
Trial drug exposure	Total dose of the drug (in mg) received during the treatment period
Number of capsules	Total number of capsules dispensed minus the total number of capsules returned
TEAE	Any adverse event with reported onset or start date after the first dose of IMP until last dose of IMP + 14 days

6.7. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not included in any analyses according to this plan will not appear in any tables or graphs but will be included only in the data listings.

Adverse events and medical history will be coded using the MedDRA version 20.1.

All medications will be coded using WHO Drug Dictionary (WHODD) v. B2 Sep2017.

A treatment related AE is any AE with a possible or probable relationship to the trial drug.

Anatomical Therapeutic Chemical (ATC) class is defined as ATC level 2. Preferred term is defined as ATC level 5.

If **partial dates** occur in the start dates of events (those observations that have both start and end dates, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

- If just **day is missing** then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later
- If just **month is missing** and the year is the same as the first dose in this OLE study, then

the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used. If the year is not the same as the first dose, then the month assigned is January

- If **both month and day are missing** and the year is the same as the first dose, then the month assigned is the month of the first dose and the day assigned is either the first day of the month or the first dose date, whichever is later. If the year is not the same as the first dose, then the date is assigned as 1 of January of the specified year

If partial dates occur in the end dates of events, the conventions are as follows:

- If just day is missing, then the day assigned is the last day of the month, or the last date of the treatment period, whichever is the earlier
- If just month is missing then the month assigned is December, unless that results in a date after the end of treatment period, in which case either the month of the treatment period is used if that results in a date within the treatment period, or otherwise the previous month
- If both month and day are missing and the year is the same as the end of the treatment period, then the date is assigned as the end of the treatment period. If the year is not the same as the end of the treatment period, then the date is assigned as 31 December of the specified year.

If **partial times** occur in the start time of events, the convention is as follows:

- If the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise
- If both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00;
- If the date is the same as the date of the first dose and only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later, and
- If the date is the same as the date of first dose and only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later.
- Otherwise the hour assigned is 12 if the hour is missing and the date is not the same as the date of first dose and the minute assigned is 30 if the date is not the same as the date of first dose.

If partial times occur in the end time of events, no times will be imputed.

These conventions will be applied only to adverse event onset dates and times with the following precaution:

- If the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Trial Patients and Demographics

7.1. Disposition of Patients and Withdrawals

The number of patients screened and who failed the screening will be summarized.

Disposition will also include tabulations of the number of patients who initiated the trial, initiated the trial on 400 mg TID dosage or 200 mg TID respectively, withdrew from trial drug and discontinued the study early (for all reasons and due to impact of COVID-19), by treatment group and overall based on SAF population.

The primary reasons for withdrawal of IMP and from the trial will also be summarized by the treatment group and overall for the SAF.

The number and percentage of patients in each analysis set (SAF and mITT) for each study center (UK, USA) and overall will also be summarized.

7.2. Protocol Violations and Deviations

Protocol deviations will be recorded in external spreadsheets maintained by the Clinical Operations group which will being viewed on an ongoing basis and finalized prior to database lock.

Incidences of protocol deviations (important, non-important, and all) will be summarized in the external spreadsheets by protocol deviation category. The number of patients with any protocol deviations as well as deviation related to COVID-19 will be summarized by counts and percentages.

All protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, age at diagnosis, ethnicity, height, weight, and BMI will be presented by treatment group and overall. Patients will be also summarized by age groups (>65 years and >75 years).

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median, maximum, 1st and 3rd quartiles will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses for demographics and baseline characteristics will be conducted for the SAF population.

The number and percent of patients reporting various medical histories, grouped by MedDRA system organ class and preferred term, will be tabulated by treatment group. This analysis will be conducted for the SAF population. Medical history will include data from in OLE study as well as transferred from IBM4809 study.

All demographics, baseline characteristics and medical history data will be listed.

7.4. Exposure and Compliance

7.4.1. Exposure

The duration of exposure to IMP will be calculated as follows: from the date of last dosing minus the first day of dosing in OLE study + 1. The exposure calculation will not take therapy interruptions into account.

Patient-years of exposure will be calculated as the sum of the above treatment durations by treatment group for the SAF divided by 365.25.

7.4.2. Calculation of capsules taken

The term dispensing period will be used to denote the period from the visit a bottle is dispensed to the following scheduled clinic visit where the same bottle is planned to be returned.

The number of capsules taken from a given bottle will generally be calculated based on the number of capsules originally dispensed in the bottle minus the number of capsules returned.

If a bottle is returned too late or not returned, some assumptions will be applied to derive the number of capsules used in the dispensing period.

- **Delayed return of a bottle:** The difference between the number of dispensed capsules and the returned capsules are assumed to have been used in the planned dispensing period (i.e. up to the first scheduled visit after the dispensing visit).
- **Non-returned bottles:** The amount of used IMP will be calculated based on the alternative assumptions:
    - **Assumption 1 (Best Case):** The planned amount of the dispensed (but non-returned) capsules is assumed to have been used in the planned dispensing period (i.e. up to the first scheduled visit after the dispensing visit).
    - **Assumption 2 (Worst Case):** None of the dispensed (but non-returned) capsules are assumed to have been used in the planned dispensing period (i.e. up to the first scheduled visit after the dispensing visit).

If a bottle is returned with more capsules that were originally dispensed in the bottle, the returned bottle will contribute with 0 (zero) capsules to the calculations (i.e. not a negative number).

7.4.3. Dose interruption and patient discontinuation

At any time during the trial, the protocol permits that the IMP may be temporarily interrupted for up to 4 weeks for an intolerable AE with supportive therapy (if needed). The interruption of the dose should be as short as possible. If the patient experiences the same intolerable AE after re-challenge with the full dose of arimoclomol, arimoclomol must be discontinued permanently.

Sites record start and stop dates of an interruption, then the sites record if patient discontinued permanently (in case of the same intolerable AE). It will be assumed the date of discontinuation is the day after stop date of the interruption.

In addition to calculating overall exposure (see above), for patients that discontinued permanently due to the same intolerable AE after re-challenge with the full dose of arimoclomol, number of days exposed will be calculated as follows: from day prior to discontinuation due to repeated intolerable AE minus the first day of dosing +1.

Length of interruption (including all reasons, and COVID-19 related reason as well) will be summarized using descriptive statistics.

7.4.4. Compliance

Overall and by visit interval treatment compliance will be determined as follows.

Compliance = 100 x (capsules taken/capsules expected to be taken) where capsules taken = number of capsules expected to be taken – number of missed capsules (regardless of reason including investigator instituted temporary halt). The expected number of capsules to be taken is calculated as:

- 6 times the number of days in the relevant period, if patient came from IBM4809 study with 1200 mg/day (400 mg t.i.d.) dosage;
- 3 times the number of days in the relevant period, if patient came from IBM4809 study with 600 mg/day (200 mg t.i.d.) dosage.

Trial drug administration data will be listed.

The number of capsules dispensed (assuming the worst case and best case separately), returned and used (assuming the worst case and best case separately), as well as treatment compliance will be summarized by treatment group, overall and by visit, for the SAF population.

7.4.5. Average daily exposure

Average daily exposure (mg) will be calculated as follows.

Average daily exposure (mg) = Average daily exposure (caps) x amount of free base (mg), where average daily exposure (caps) = sum of total exposure doses (caps) during the treatment divided by the duration of exposure.

Average daily exposure will be summarized using descriptive statistics.

7.5. Baseline Columbia Suicide Severity Rating Scale (C-SSRS)

Baseline characteristics will be tabulated for Suicidal Ideation and Suicidal Behavior separately. Assessment performed at Visit 14/Month 20 of the blinded IBM 4809 trial will be served as the baseline evaluation for this OLE study.

All results from the C-SSRS will be listed.

8. Safety and Tolerability Analysis

Safety and tolerability will be evaluated from reported AEs, clinical safety laboratory values (haematology and clinical chemistry), vital signs, ECG evaluation, and C-SSRS.

All safety analyses will be performed on the SAF population unless otherwise specified.

8.1. Adverse Events

Adverse events (AEs) will be coded using the MedDRA version 20.1 dictionary.

AEs after the first dose of IMP until the last dose of IMP +14 days will be considered treatment-emergent adverse events (TEAEs).

Adverse events that start or continue inside the OLE timeline only will be summarized and listed. AEs that started and finished before 1st dose in the OLE study, but were transferred from main 4809 study won`t be presented.

The overall table of the incidence of AEs will summarize number and percentage of patients, number of AEs and TEAEs as well as rate in following categories: with any adverse event; mild, moderate and severe AEs and TEAEs; AEs and TEAEs related to study drug, serious AEs and TEAEs; serious AEs and TEAEs related to study drug; AEs and TEAEs leading to temporary interruption of IMP and AEs as well as TEAEs leading to treatment discontinuation by treatment groups and overall. Number of patients as well as observation time (years) will be tabulated.

The table with number and percentage of patients with TEAEs, grouped by MedDRA system organ class (SOC) and preferred term (PT), will be summarized by treatment group and overall. In the case of multiple occurrences of the same event within the same subject, each subject will only be counted once for each SOC or PT.

The incidence of TEAEs (number and percentage of patients with TEAEs), will also be summarized by severity and relationship to IMP.

In the summaries showing severity and relationship to IMP at each level of summarization (SOC and PT), patients who reported more than one treatment-emergent adverse event will be counted only once for the maximum severity (mild, moderate, severe) and strongest relationship (not related, possibly related, probably related).

If a particular event is missing the severity and/or relationship, then the strongest possible severity and/or relationship will be assumed for analysis (severity = severe, relationship = probably related) and be tabulated. In the listings the raw (non-imputed) values of severity or relationship will be presented.

Any abnormal clinical significant physical examination findings will be recorded as AEs, according to Investigator`s request.

No inferential statistical tests will be performed.

8.2. Adverse Events Leading to Withdrawal

Summaries of TEAEs leading to withdrawal of IMP, by treatment group, SOC, and PT will be prepared for the SAF population. No inferential statistical tests will be performed.

A data listing of TEAEs leading to withdrawal of IMP will also be provided, displaying details of the event(s) captured on the CRF.

8.3. Serious Adverse Events and Deaths

Serious treatment emergent AEs as well as death will be listed.

Serious treatment emergent AEs will also be tabulated by SOC and PT and presented by treatment for the SAF population. The summary for deaths will be also presented.

8.4. Clinical Laboratory Evaluations

For each in-person visit, except for the Baseline visit, the following lab procedures will be performed:

- Haematology with differentials: haemoglobin, haematocrit, mean corpuscular volume (MCV), red blood cells (RBC/erythrocytes), white blood cells (WBC/leukocytes), and differential count (basophils, eosinophils, lymphocytes, monocytes, neutrophils [% and absolute count], and platelets).
- Clinical chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), bilirubin (total), calcium, chloride, cholesterol, creatine kinase, creatinine, gamma-glutamyl transferase (GGT), glucose (random), iron, lactate dehydrogenase (LDH), phosphate, potassium, protein total, sodium, triglycerides, BUN, uric acid
- Other: cystatin C.

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each haematology, clinical chemistry parameter and cystatin C as well. Each measurement (continuous data) will be classed as below (low), within (normal), or above (high) normal range, based on ranges supplied by the laboratory used.

Local laboratory results will be used for the analysis in case subject cannot attend the trial site for close observation in relation to elevated transaminases. All local laboratory results will be flagged in the data listings.

Laboratory test results will be listed. Laboratory values that are outside the normal range will be flagged in the data listings. Listings of patients with parameter results considered to be clinically significantly abnormal by investigator will be presented. The listings will include all lab parameter results where at least one value is considered clinically significantly abnormal.

The incidence of patients fulfilling the below criteria will be summarized by visit and for the whole study:

- Post baseline sCr value ≥ 1.5x baseline value

- Post-baseline sCr value ≥ 2x baseline value
- Post-baseline sCr value ≥ 3x baseline value

The incidence of patients fulfilling the below criteria will be summarized:

- ALT ≥ 3 × ULN
- ALT ≥ 5 × ULN
- ALT ≥ 8 × ULN
- ALT ≥ 20 × ULN
- AST ≥ 3 × ULN
- AST ≥ 5 × ULN
- AST ≥ 8 × ULN
- AST ≥ 20 × ULN
- ALT or AST ≥ 3.0x ULN
- ALT or AST ≥ 5.0x ULN
- ALT or AST ≥ 8x ULN
- ALT or AST ≥ 20 × ULN
- Total Bilirubin≥ 2x ULN
- ALP ≥ 2 x ULN
- ALP ≥ 3 × ULN
- (ALT or AST ≥ 3.0x ULN) and Total Bilirubin≥ 2x ULN and ALP ≤ 1.5x ULN
- ALT ≥ 3 × ULN & Total Bilirubin ≥ 2 × ULN & ALP ≤ 1.5 × ULN
- AST ≥ 3 × ULN & Total Bilirubin ≥ 2 × ULN & ALP ≤ 1.5 × ULN

The above categorical parameters are to be presented in one table for “by visit” and one table for “overall” summaries, respectively.

Number (%) of patients that have potentially clinically significant laboratory values overall and by visit will be presented.

Plots of all mean ALT, AST, ALP, LDH, GGT, total bilirubin, creatinine, creatine kinase, and Cystatin C Results with error bars, that represent +/- 1 x standard error of the mean will be presented over the time, separately by treatment group.

8.5. Vital Signs

Descriptive summaries of mean values and changes from baseline will be calculated for weight, heart rate, respiratory rate, and sitting blood pressure by treatment group and by visit using the SAF population.

Vital signs will be listed.

8.6. Electrocardiograms

The number and percentage of patients with normal, abnormal (not clinically significant) and abnormal (clinically significant) ECG results will be summarized by visit and overall, by treatment group using the SAF population.

ECG results (normal/abnormal) will be listed. Clinically significant abnormalities will be flagged.

8.7. Physical examination results

No physical examination data will be presented. The investigators have been asked to record abnormal clinical significant results as AEs.

8.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be tabulated by treatment group and by visit displaying only the highest category for each patient for the SAF.

Baseline characteristics will further be tabulated for Suicidal Ideation and Suicidal Behavior separately.

All results from the C-SSRS will be listed.

8.9. Concomitant Medication

Prior medications will be presented separately from concomitant medications.

Medications that started prior to the start of the trial drug in this OLE study will be considered prior medications whether or not they were stopped prior to the first dose of trial drug. Medications continuing or starting post the first dose of trial drug in this OLE study will be considered to be concomitant, regardless they were before the last dose of IMP or after. If a medication starts prior to the first dose of trial drug and continues after the first dose of trial drug, it will be considered both prior and concomitant.

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages for the SAF. Medications will be coded using WHODD v. B2 Sep2017.

9. Changes from Planned Analysis and clarifications

The analyses presented in the SAP were accustomed to the study requirements due to early termination of the study. The changes are the following:

- The analysis of the mTUG endpoint has been adapted to be conducted on reciprocal values multiplied with the planned distance of 6 meters in order to appropriately reflect and handle values missing due to inability of patients to initiate the test (not related to external circumstances). This corresponds approximately to analysing the velocity with which the mTUG route of 6 meters is accomplished, including the time spent for standing up and sitting down again.
- [redacted]
- Due to early study termination by the Sponsor the planned analysis was revised: no testing of efficacy hypothesis to be performed in this OLE study, but the data supposed to be used for efficacy will be summarized at each visit and change from baseline using descriptive statistics. The focus of the analyses was moved to safety endpoints. All exploratory endpoints, as well as any PK assessments, won`t be analyzed

10. Other Planned Analysis

10.1. Pharmacokinetic Analysis

No PK/PD data will be summarized or listed due to early termination of study by the Sponsor and revised study objectives and endpoints.

11. References

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5. Ratitch, O'Kelly, Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures. PharmaSUG2011, Paper SP04
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8. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.
9. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press. 2010.
10. THE HEALTH ASSESSMENT QUESTIONNAIRE (HAQ) DISABILITY INDEX (DI) OF THE CLINICAL HEALTH ASSESSMENT QUESTIONNAIRE (VERSION 96.4).

12. Tables, Listings, and Figures

All listings, tables, and figures, including presentations by region, are specified in a separate shells document. The shells are to be considered for guidance only, and minor deviations from the shells are acceptable as long as the outputs are consistent with the text of this SAP.

Appendix 1: Abbreviations List

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
BMI	Body Mass Index
CRF	Case Report Form
CS	Clinically Significant
CTR	Clinical Trial Report
C-SSRS	Columbia Suicide Severity Rating Scale
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HR	Heart Rate
IBM	Inclusion Body Myositis
IBMFRS	Inclusion Body Myositis Functional Rating Scale
ICH	International Council for Harmonization

Abbreviation	Definition
ID	Identification
IMP	Investigational Medicinal Product
mITT	Modified Intent-To-Treat
KUMC	University of Kansas Medical Center
LDH	Lactate Dehydrogenase
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
mTUG	Modified Timed Up and Go
MVICT	Maximal Voluntary Isometric Contraction Testing
N	Number
OLE	Open-label
PD	Pharmacodynamics
PK	Pharmacokinetic
PKAP	Pharmacokinetic Analysis Plan
RBC	Red Blood Cells
RR	Respiratory Rate or Relative Rate
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS®	A Software System Used for Data Analysis

Abbreviation	Definition
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
T.I.D.	Three times a day
WBC	White Blood Cells
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
UCL	University College London