Clinical trial of Zoledronic acid (Aclasta) in children and adolescents with Duchenne muscular dystrophy

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Statistical Analysis Plan

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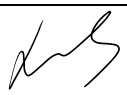
9th July 2020	1.0	Xiaofang Wang and Katherine Lee		Initial release.	Not applicable.

Statistical Analysis Plan Approval Page

Study: Clinical trial of Zoledronic acid (Aclasta) in children and adolescents with Duchenne muscular dystrophy

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The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner, i.e. without knowledge of the effect of the intervention(s) being assessed.

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1 Study synopsis

This is a parallel 2-arm randomised multi-centre trial comparing zoledronic acid plus oral vitamin D and calcium versus oral vitamin D and calcium alone in 60 boys with Duchenne muscular dystrophy (DMD) from four hospitals. To demonstrate whether intravenous zoledronic acid administered every 3-6 months plus oral vitamin D and calcium demonstrates superiority relative to vitamin D and calcium alone for a change in lumbar spine (LS) areal bone mineral density (BMD) and bone mineral apparent density (BMAD) Z-score at Month 24 relative to baseline, and thus whether such a treatment regimen has the potential to reduce the fracture risk in boys with DMD.

Title	Clinical trial of zoledronic acid (Aclasta) in children and adolescents with Duchenne muscular dystrophy
Objectives	To show that zoledronic acid plus calcium and vitamin D is superior to calcium and vitamin D alone, to increase BMD, and reduce fracture at 24 months
Design	Open label randomized
Outcomes	Change in BMD and BMAD Z-score (primary outcomes), and bone turnover markers, at 12 and 24 months compared with baseline, and fracture rate within 24 months
Study duration	36 months
Intervention	Zoledronic acid
Number of subjects	30 in each arm (60 total)
Population	Boys aged 6-16 who have Duchenne muscular dystrophy
Study locations	The Royal Children's Hospital (RCH), VIC Princess Margaret Hospital Perth (PMH), WA The Children's Hospital at Westmead (CHW), NSW The Liggins Institute, Auckland (Liggins), NZ

1.1 Study objectives

1.1.1 Primary objective

To demonstrate that zoledronic acid plus oral vitamin D and calcium is superior to oral vitamin D and calcium for increasing the LS areal BMD and BMAD Z-score at Month 24 relative to baseline.

1.1.2 Secondary objectives

- To evaluate between-treatment differences in the change from baseline in LS areal BMD Z-score, LS and total body bone mineral content (BMC), and bone turnover markers at 12 and 24 months.

- To evaluate between-treatment differences in the change from baseline in tibial metaphyseal BMC and volumetric BMD (vBMD) and diaphyseal BMC, vBMD and cross-sectional area on peripheral quantitative computed tomography (pQCT) at 12 and 24 months.

- To evaluate between-treatment differences for the proportion of patients with new vertebral and long bone fractures and for vertebral morphometry at Month 12 and 24 since baseline.

Exploratory efficacy objectives:

- To evaluate between-treatment differences in change in height Z score and the percent change in distal femur BMD at Month 12 and 24 relative to baseline.

- To evaluate between-treatment differences in the number of patients with new clinical fractures at Month 12 and 24 since to baseline.

Safety objective
To obtain short term safety data on the use of intravenous zoledronic acid for the treatment of boys with DMD treated with glucocorticoids through the monitoring of relevant clinical and laboratory safety parameters.

1.2 Patient population

1.2.1 Inclusion criteria:

- All boys between 6 and 16 years with confirmed DMD and who are receiving at least 3 months of daily glucocorticoid therapy

- Lumbar spine dual-energy X-ray absorptiometry (DXA) scan Z-score or whole body DXA scan Z-score is <-1.

1.2.2 Exclusion criteria:

- Genant Grade 3 or greater vertebral compression

- Any prior use of osteoporosis or bone-modifying therapy, such as bisphosphonates, sodium fluoride, calcitonin, calcitriol, antiepileptic medication, luteinizing hormone-releasing hormone (LHRH) agonists or Growth Hormone (GH)

- Patients who have received testosterone therapy may only be included in the trial if this therapy was given as part of physiological replacement in the setting of documented hormonal deficiencies

- Any prior history of malignancy

- Any medical condition that might interfere with the evaluation of LS BMD, such as severe scoliosis or spinal fusion. Patients with less than 3 evaluable vertebrae by DXA evaluation in the region of

interest (ROI) L1-L4, as confirmed by the central imaging laboratory, will not be considered eligible for this study.

- Hypocalcaemia and hypophosphatemia: any value (age-matched) below the normal range at screening

- Vitamin D deficiency (serum 25-hydroxy vitamin D concentrations of < 50 nmol/L) at screening. If patient is deficient, and management of low vitamin D is possible to bring levels to >50nmol/L, patient will then become eligible again.

- Renal impairment: GFR < 35 ml/min/1.73 m2 at screening based either on the Schwartz formula or Cystatin C.

- If the Schwartz formula is used, a serum creatinine increase between Visit 2 and Visit 3 greater than 44.2 umol/L

- History of hyperparathyroidism, hypothyroidism or hyperthyroidism within 1 year of screening

- History of sarcoidosis, primary bone disease (osteogenesis imperfecta, idiopathic juvenile osteoporosis, rickets/osteomalacia), Kawasaki's disease or Henoch-Schonlein Purpura.

- Diagnosis of active uveitis (symptomatic or asymptomatic) at the time of enrolment in the study.

- Any subject involved in another study, if an investigational agent is deemed by investigators to possibly interfere with this study agent. (for example, use of a different bisphosphonate or a statin, a drug that utilises the same biochemical pathways)

1.3 Outcomes

1.3.1 Primary outcome

- Change in LS areal BMD Z-score and BMAD (BMC divided by the volume of 4 lumbar vertebrae, L1-L4) at Month 24 compared with baseline.– It was realised during the trial that changes in height and volume of vertebrae for these boys over the 24 month study period is negligible - partly due to chronic glucocorticoid use, and for many, fixed flexion deformity of limbs. This means that there is little need to account for changes in vertebrae volume from baseline. Therefore, although change in BMAD was also a primary outcome of this study, it will no longer be analysed and will not be included in the paper.

1.3.2 Secondary outcomes

- Change from baseline in LS areal BMD Z-score, LS and total body BMC and in bone turnover markers at 12 and 24 months. Bone turnover markers include: alkaline phosphatase (ALP), crosslinked C-telopeptide (CTX), procollagen type 1 N-terminal propeptide (P1NP), osteocalcin, calcium, parathyroid hormone (PTH), and 25-hydroxyvitamin D (25(OH)D).

- Change from baseline in tibial metaphyseal BMC and vBMD, and diaphyseal BMC, vBMD and cross-sectional area on pQCT at 12 and 24 months.

- Proportion of patients with new vertebral and long bone fractures and vertebral morphometry at Month 12 and 24 relative to baseline.

1.3.3 Safety outcomes

- Nil

1.3.4 Exploratory outcomes

- Change in height Z score and the percent change in distal femur BMD at Month 12 and 24 relative to baseline. – As mentioned above, the changes in height for these boys over the 24 month study period is negligible. We also found it is very difficult to position participants distal femur and keep it flat. This made the DXA measurement at distal femur impossible. Given these issues, these two outcomes will no longer be analysed and will not be included in the paper.

- Number of patients with new clinical fractures at Month 12 and 24 relative to baseline.

1.3.5 Additional outcomes also of interest (not in the original protocol)

- Changes in LS BMD and height adjusted LS BMD Z score at 12 and 24 months, relative to baseline.

- Change from baseline in radial metaphyseal BMC and vBMD, and diaphyseal BMC, vBMD and cross-sectional area on pQCT at 12 and 24 months.

- Changes in pain scores (measured by Wong-Baker Pain faces pain score) and walking ability (measured by wheelchair use and 6-minute walk test) at 12 and 24 months, relative to baseline.

1.4 Intervention

Active arm – Zoledronic acid at 0, 3, 6, 12 and 18 months plus Calcium and Vitamin D.
Control arm – Calcium and vitamin D only.

Vitamin D and calcium treatment will be provided at the daily dose 1200mg of calcium and 1000 units of cholecalciferol per patient. These doses are comparable to published guidelines and will act as a supplement to dietary intake. These treatments will be provided as an ongoing integral part of standard good clinical care for all patients, with compliance assessed by tablet counting by researchers at each clinic visit.

We will induce puberty, as a clinical indication for all those who are 14.5 years and older and who have not already clearly started spontaneous puberty, using an oral testosterone derivative, testosterone

undecanoate, in a dosing schedule that is identical for all ages and all sites (Testosterone capsules (Andriol®) at 40mg/day for 6 months then 80mg/day for 12 months).

Zoledronic acid for IV administration - 5.0 mg/100 ml solution, supplied in a ready-to-infuse plastic bottle, by Novartis, prepared and administered by nursing staff in ambulatory care ward according to standard protocols – over 20-30 minutes in 50-60ml normal saline.

Calcium 1200mg and vitamin D 1000 IU to be commenced at Visit 2 (first infusion for boys in Group A).

Treatment Arm	# of Patients Entered Treatment	Type of Study Drug	Compound	Daily dose given	Max daily Dose	Frequency	Route	Generic Acceptable? (applies only for comparator)
Active	30	Investigational	Zoledronic acid	0.025 mg/kg for first 2 doses then 0.05mg/kg/dose for remaining 3 doses	5mg	At time 0, 3, 6,12 and 18 months	IV	No
		Co-Therapy	Calcium Vitamin D	1200mg 1000 IU	1200 mg 1000 iu	Daily for 24 months	Oral	Yes
Control	30	Control	none					
		Co-Therapy	Calcium Vitamin D	1200mg 1000 IU	1200 mg 1000 iu	Daily for 24 months	Oral	Yes

Below table shows the study visits and procedures schedule.

Visit	Screening	0 month	3 month	6 month	12 month	18 month	24 month
Visit no #	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Time for visit	2.5 hrs	2 hrs	2 hrs	2 hrs	2.5 hrs	2 hrs	2.5 hrs
Medical check up	•	•	•	•	•	•	•
Dental check up	•						
Zoledronic acid infusion (Group A only)		•	•	•	•	•	
Blood test	7 ml	1 ml (Group A only)	3 ml	7 ml	7 ml	7 ml	7 ml
Bone density (DXA)	•				•		•
pQCT	•				•		•
Bone age x-ray	•				•		•
Wong-Baker FACES pain scale	•		•	•	•	•	•
6 minute walk test	•				•		•
Back x-ray (only if not taken as part of standard care)	•				•		•
Medications (calcium & vitamin D)		•	•	•	•	•	
Medications (calcium & vitamin D booster)		• (Group A only)					
Medications (phosphate)		• (Group A only)	(Group A only – use extra phosphate as necessary for hypophosphatemia after infusions)				

Specific to Group A (Zoledronic acid)

Note: Wong-Baker FACES pain scale is only analysed at screening, 12 months and 24 months.

1.5 Randomisation and blinding

Randomisation will be achieved using minimisation (a highly efficient method accounting for strata, especially when the sample sizes are small). Recruitment will be stratified by age (<12 years or 12-16 years) and centre. Randomisation will be achieved via an automated telephone-based system via the NHMRC

Clinical Trials Centre, University of Sydney. This, together with minimisation, will ensure allocation concealment for the study.

The Clinical Epidemiology and Biostatistics Unit (CEBU) at the Murdoch Children's Research Institute (MCRI) will provide statistical support. All data will be analysed by Dr Xiaofang Wang with support from Prof Katherine Lee – see data analysis section below.

Blinding arrangements will not be applied to the administration of the drug, as the administration of zoledronic acid is by intravenous infusion and other medications are oral. Intravenous cannulation is uncomfortable and anxiety provoking for children, particularly when weight is a problem, as is the case for many of the boys with DMD. It would not be ethically acceptable to use either a placebo solution for the control group. De-identified data will be entered into a secure database to allow for analysis of anonymous data between the four institutions.

1.6 Sample size

Sample size of 30 patients for any study of bone density has previously been calculated by Professor John Wark and has been accepted for all previous studies of bone density assessment in both children and adults. This number of subjects gives an 80% chance of seeing a 2% difference in BMD.

An alternative accepted method is as follows (From: J Peat the Health Science Research Handbook for Quantitative Methods *Allen & Unwin* 2001):

- To give 80% chance of seeing a 0.5 SD change in BMD, 34 subjects per group is needed. To give 90% chance of seeing a 0.5 SD change in BMD, 50 per group is needed.

- To give 80% chance of seeing a 0.75 SD change in BMD, 16 subjects per group is needed. To give 90% chance of seeing a 0.75 SD change in BMD, 24 per group are needed.

We anticipate seeing increases of 10-40% in BMD over 12 months in 30 zoledronic acid treated subjects, based on previous studies of Zoledronic acid in other bone fragility conditions, including corticosteroid use. Sample calculation is impossible for fracture frequency as it is dependent on multiple factors such as mobility and falls.

2 Statistical analysis

2.1 Analysis principles

- Analysis will be conducted using an intention to treat analysis (primary analysis) and per-protocol analysis.
- We will also conduct a sensitivity analysis where we will restrict the analysis to patients without vertebral fracture in the scanning area (L1 to L4).
- Missing data handling: It is expected that less than 10% of data will be missing, hence the primary analysis will be a complete case analysis. However as a secondary analysis, a mixed model analysis will be conducted on primary and secondary outcomes applied to all outcome timepoints simultaneously (including baseline) which naturally accounts for the missing data as it enables all

participants with at least one measurement to be included in the analysis, which will mean mean all participants are included as we are expecting no missing data at baseline.

- STATA will be used to conduct all analyses.

2.2 Interim analyses

Nil

2.3 Blind review

Nil

2.4 Data sets analysed and subject disposition

- Intention to treat population – all randomised subjects will be analysed in the arm that they were randomised to
- Per-protocol population – all those who completed the study according to the protocol (this population will exclude participants who did not have their complete dose of zoledronic acid and who did not have their complete dose of vitamin D and calcium)

2.5 Patient characteristics

The baseline characteristics of participants will be presented for each group and will be described using means and standard deviations (or medians and interquartile ranges for non-normal data) for continuous data and proportions for categorical data.

Baseline characteristics (all continuous variables unless specified)

- Age at randomisation
- Bone age and age at screening
- Age at diagnosis
- Study centre (RCH, PMH, CHW, Liggins)
- Wheelchair usage at screening (Y/N)
- Weight at screening
- BMI at screening
- Type of steroid (deflazacort vs prednisolone)
- Dosage (average daily dose) and duration (between start date and screening date, in years) of each type of steroid
- Pre-existing fractures at start of the study (Y/N and number of fractures)
- Baseline puberty level (binary: 0/1)
- Baseline Calcium, ALP, CTX, P1NP, 25(OH)D and PTH levels
- Other medications at screening (ACE inhibitors: Y/N; antidepressants: Y/N)
- Other medical conditions at screening (Y/N)

Baseline pQCT results at 4% and 66% site of tibia and radius (all continuous)

- Total BMC raw and Z-score at 4%
- Cortical BMC raw and Z-score at 66%
- Total vBMD raw and Z-score at 4% and 66%
- Trabecular vBMD raw and Z-score at 4%
- Cortical vBMD raw and Z-score at 66%
- Total CSA raw and Z-score at 4% and 66%
- Cortical CSA raw and Z-score at 66%
- Proportion of cortical/total CSA raw and Z-score at 66%
- Cortical thickness raw and Z-score at 66%
- Periosteal circumference (measured and circular) at 4% and 66%
- Endosteal circumference (measured and circular) at 66%
- Stress strain index and Z-score at 66%

Baseline DXA results at LS and total body (all continuous)

- LS areal BMD raw and Z-score (with and without height adjustment)
- LS BMC
- Total body BMC

Baseline blood test results (all continuous)

- ALP, CTX, P1NP, Osteocalcin, Calcium, PTH and 25(OH)D

2.6 Analysis of compliance and concomitant therapies

Data on compliance and concomitant therapies will be described separately in the two treatment groups as described below.

2.6.1 Compliance

- Cumulative exposure to the intervention by 24 months (calculated as a product of dose and duration summarised as a mean, standard deviation and range): zoledronic acid, VitD, Calcium.
- Average individual compliance: as per pharmacy logs - %tablets taken over the 24 month study period summarised as a mean, standard deviation and range.
- Reasons for lack of compliance (number for each reason)

2.6.2 Protocol violations

Number of participants with one or more protocol violations including:

- those who missed the injection of zoledronic acid
- those who did not take the complete dose of vitamin D and calcium

2.6.3 Concomitant therapies

Concomitant Medications / Conditions outside of those that are part of the study

- Other medications taken by subjects during the 24 month study period reported as number and proportion of participants by medication.

- Other conditions developed during the 24 month study period reported as number and proportion of participants by condition.

Concomitant Medications related to study (presented as the number and proportion of participants with each at any time during the 24 month study period)

- Incidence of vitamin D stoss dose supplementation
- Incidence of paracetamol supplementation
- Incidence of ibuprofen supplementation

2.7 Analysis of the primary outcome

2.7.1 Main analysis

The primary efficacy variable, change from baseline in LS areal BMD Z-score at 12 and 24 months, will be calcuated as the value at 12 or 24 months minus value at baseline, and will be summarised by treatment group. Given the measure in a Z-score the unit of change will be SD. The difference between the changes in the two treatment groups will be expressed as mean difference and its 95% confidence interval (CI) obtained using a linear regression model applied to the change, adjusted for age at randomisation, steroid duration (<3 months or ≥ 3 months) and centre as covariates. We will also compare outcomes at 12 and 24 months using a mixed model applied to the data at baseline, 12 months and 24 months with fixed effects for treatment (at 12 and 24 months), age at randomisation (<12 years or 12-16 years) and centre, and a random effect to allow for the repeated measures for each individual. The parameters of interest will be the treatment effect at 12 and 24 months.

2.7.2 Adjusted analyses

Nil.

2.7.3 Subgroup analyses

Nil.

2.7.4 Other sensitivity analyses

The presence of vertebral fractures (on L1 to L4) is likely to cause an apparent increase in LS BMD due to the compression of the vertebrae. Given this we would ideally conduct a sub-group in those with and without vertebral fractures. Considering the small sample size and low fracture rates, we will instead run a sensitivity analysis of the primary outcome to see whether the results will change after removing those with incident vertebral fractures during the follow up. These comparisons between groups will be made by using the same analysis specified in 2.7.1 with the presentation of results as a mean difference and 95% CIs.

2.8 Analysis of secondary outcomes

2.8.1 Bone, blood and pain outcomes

Changes from baseline to 12 months and 24 months for the variables list below (except Z-scores and pain score) will be calculated as a percentage change using the baseline value as the denominator. For Z-scores and pain score, changes will be calculated as the value at 12 or 24 months minus value at baseline. The difference between the changes in the two treatment groups will be expressed as mean difference and its 95% CIs obtained using a linear regression model, adjusted for age at randomisation (<12 years or 12-16 years) and centre as covariates. Outcomes at each time point will also be compared between the groups using a mixed model applied to the baseline, 12 month and 24 month data as described for the primary outcome.

2.8.1.1 DXA outcomes at LS and total body

- LS BMD
- Height adjusted LS BMD Z-score
- LS BMC
- Total body BMC

2.8.1.2 pQCT Outcomes at tibia and radius (data are in a separate excel file)

- Total BMC raw and Z-score at 4%
- Cortical BMC raw and Z-score at 66%
- Total vBMD raw and Z-score at 4% and 66%
- Trabecular vBMD raw and Z-score at 4%
- Cortical vBMD raw and Z-score at 66%
- Total CSA raw and Z-score at 4% and 66%
- Cortical CSA raw and Z-score at 66%
- Proportion of cortical/total CSA raw and Z-score at 66%
- Cortical thickness raw and Z-score at 66%
- Periosteal circumference (measured and circular) at 4% and 66%
- Endosteal circumference (measured and circular) at 66%
- Stress strain index and Z-score at 66%

2.8.1.3 Blood test results

- ALP
- CTX
- P1NP
- Osteocalcin
- Calcium
- PTH
- 25(OH)D

2.8.1.4 Pain outcome

- Wong-Baker Pain faces pain score – It is a self-reported of pain scale on a range of 0-10 and will be analysed as a continuous variable.

2.8.2 Fracture outcomes

Fracture outcomes will be summarised as absolute number of fractures and number and proportion of individuals with one or more fractures in each treatment group. A comparison of these outcomes between the groups will be made using logistic regression adjusted for stratification factors used at randomisation. The fracture outcomes of interest are:

- Long bone fractures *(variable in PTNA)*
- Crush fractures (variable available in *a separate excel spreadsheet)*

In addition, vertebral height of crush fractures will be summarised as mean Genant score and mean spinal deformity index (SDI) for patients with crush fractures by group, with group comparison using linear regression adjusted for age at randomisation (<12 years or 12-16 years) and centre. *These data will come in a separate excel spreadsheet rather than the PTNA database*

2.8.3 Mobility outcomes

The following outcomes will be analysed as described:

- The %time spent in wheelchair ranged between 0 and 4, where 0 = no wheelchair use, 1 = <25%, 2 = 25-50%, 3 = 50-75%, 4 = >75% time spent in wheelchair. Two binary variables will be derived for: 1) progress to wheelchair from walking; 2) an increase in the %time spent in wheelchair at 24 months compared to baseline. The number of patients and proportions of "yes" on these two binary variables will be reported in each group. Results will also be reported separately by age group (<12 years or 12-16 years). Comparisons between groups will be made using logistic regression models, with results presented as odds ratios and 95% CIs, adjusted for age at randomisation (<12 years or 12-16 years) and centre.

- The number and proportion of patients are non-ambulatory will be reported and compared between groups at 12 and 24 months using logistic regression models, with results presented as odds ratios and 95% CIs, adjusted for age at randomisation (<12 years or 12-16 years) and centre. For those who can walk, a 6-minute walk test will be done and distance travelled in the test at 12 and 24 months will be analysed using change from baseline and the method specified under 2.8.1. *(variables in PTNA)*

2.9 Analysis of safety outcomes

2.9.1 Adverse events

ZA Infusion Adverse Events

Incidence of the following events during the study period in ZA group (from recruitment to 24 months, especially at 48 and 72 hr postinfusion):

- hypo-calcaemia (less than 2.0 mmol/L)
- hypo-phosphatemia (less than 0.6mmol/L)

will be presented using the absolute number of events, as well as the number and proportions of participants with the event.

2.9.2 Laboratory data and vital signs

Nil.

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Appendix 1: Proposed tables and figures

Instructions: It can be very useful to include dummy tables to provide a clear guide for how the results will be presented.Below is a list of common tables, figures and listings typically produced in a randomised clinical trial; however, they are neither exhaustive nor applicable to every trial. When designing dummy tables, a good principle is to be as specific as possible to remove possible interpretation errors. Ways to do so include adding footnotes to the tables, direct clarifying notes to the programmer/statistician who will be responsible for the analysis as well as providing statistical code.

For examples of dummy tables, please refer to the library located on the ACTA STiNG webpage.

Figure 1: **Consort flowchart**

Table 1: **Baseline characteristics**

Table 2: **Baseline medical history**

Table 3: **Compliance to intervention**

Table 4: **Reasons for discontinuing intervention**

Table 5: **Protocol deviations**

Table 6: **Concomitant therapies**

Table 7: **Physiological and laboratory values during the study period**

Figure 2: **Longitudinal mean plot of <variable>**

Table 8: **Analysis of primary outcome**

Figure 3: **Forest plot for subgroup analysis of primary outcome**

Figure 4: **Kaplan-Meier plot of time to <enpoint>**

Table 9: **Continuous and binary secondary outcomes**

Table 10: **Adverse events**

Listing 1: **Protocol deviations**

Listing 2: **Adverse drug reactions**