Section 1: Administrative Information

Title:

Weight loss as treatment for gout in patients with concomitant obesity: Statistical Analysis Plan for a proof-of-concept randomized controlled parallel-group trial

Trial registration:

VEK: H-18007292

WWW.ClinicalTrials.gov: NCT03664167

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(RC)
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Protocol version

This document has been written based on information contained in the study protocol version dated 18 September 2018.

SAP revisions

None.

The authors (countries) of this SAP includes

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Roles and responsibility

All authors have contributed by writing, reviewing, and approving the SAP for this trial.

All contributors agree to be accountable for all aspects of the SAP.*Co-first authoring.

Section 2: Introduction

Background and rationale

Gout is an increasingly common disorder[1] characterized by elevated serum urate (SU) and by acute and chronic arthritis causing severe disability and pain. Long-term management of gout focuses on urate-lowering therapy (ULT) and keeping SU under its solubility threshold. When SU is kept under the threshold for solubility, the frequency of gout flares will decrease, and the urate crystals dispositioned in the joints will dissolve. New therapeutic management of gout has in recent years emerged. However, despite the potential for effective treatment, gout management remains suboptimal[2] According to the overarching principles, and latest EULAR recommendations - emphasizing the need to address comorbidities - in the management of gout, every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including kidney impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, smoking, hyperlipidemia, hypertension, diabetes, and obesity[3,4]. Appropriate management of these comorbidities is an integral part of the management of gout[2]

Epidemiological data link obesity and other components of the metabolic syndrome to the development of gout. Both conditions share pathogenetic mechanisms and the development of one disease increases the risk of the other and may trigger the onset of a vicious circle[5]. In addition, insulin resistance (IR) has been closely connected to gout[6]. Insulin stimulates the renal tubular sodium hydrogen exchanger facilitating secretion of hydrogen and reabsorption of not only sodium, bicarbonate, and chloride but also organic anions such as urate. This constitutes a putative mechanism by which IR and hyperinsulinemia cause hyperuricemia[7,8]. However, the hypothesis that a beneficial effect of weight loss in these patients is caused by a change in insulin resistance is currently controversial[9]. Hypertension and dyslipidemia as part of the metabolic syndrome has been linked to gout. Epidemiological studies support the alleged association between SU and hypertension and find that uric acid is an independent risk factor for developing hypertension. Consistency is found in a large number of prospective observational studies[10–17]. Gout has also been associated with both increased very-low-density lipoprotein (VLDL) triglycerides[18,19] as well as low levels of high-density lipoprotein (HDL)-cholesterol[20]. In hyperuricemic individuals there is also a strong linear relation between, total cholesterol, triglycerides, LDL cholesterol and apolipoprotein-

B levels and an inverse relationship with HDL and SU[21]. A causal link between gout and hypertension/gout and dyslipidemia has yet to be discovered.

There is some physiological evidence, although sparse, that weight loss in patients with gout reduces both SU and number of gout flares[22,23]. Despite the scarcity of data regarding the effects of weight loss in gout, international guidelines recommend dietary intervention and weight loss as a core management strategy in patients with concomitant gout and obesity[24]. Medical treatment strategies have focused on either treatment of the acute inflammatory response of flares or long term reduction of SU by either inhibiting its production with xanthine oxidase inhibitors or increase renal excretion with uricosuric agents[24]. To date, no treatment strategy has targeted the basic dysmetabolic mechanisms linking obese patients with gout.

The Parker Institute has previously designed and applied a well-documented weight loss program running over 16 weeks (CAROT study) that effectively results in a significant weight loss (average ~12% of body weight) in obese (body mass index [BMI] >30 kg/m2) patients with knee osteoarthritis with beneficial improvements in knee pain and function[25–28]

Aims

To explore the short term clinical and laboratory effects related to a rapid diet-induced weight loss in obese individuals with gout compared to an unblinded control group. The aim with the current study is to address whether obese gout patients are able to reduce their body weight, leading to a reduction in SU levels, with an improvement in pain and fatigue. We will also explore whether there are any significant adverse events related to an intensive weight loss program in these individuals.

Hypotheses

The group undergoing the intensive diet will lose more weight than the group that "only" follow the conventional diet. The weight loss will mediate lower urate levels which will improve the clinical outcomes in these individuals.

Objectives

Primary efficacy objective: To compare the effect of intensive weight loss, relative to the control group, on changes in body weight from baseline to week 16, in patients with gout and concomitant obesity.

Key secondary efficacy objectives: To compare the effect of intensive weight loss, relative to the matched control group, on changes in serum urate, changes in VAS-fatigue, and changes in VAS-Pain from baseline to week 16, in patients with gout and concomitant obesity.

Other secondary objectives: To explore the effect of the intensive weight loss, relative to the matched control group, on all the following exploratory secondary outcomes:

- proportion of participants maintaining serum urate levels <6mg/dL at visit week 8 and week 16
- percentage reduction in serum urate (%) at final visit (week 16)
- the proportion of individuals with any gout flare in the FIRST 8 weeks following randomization
- the proportion of individuals with any gout flare in the LAST 8 weeks following randomization
- the number of gout flares during the trial period for each patient (up to week 16)
- change in functional status (HAQ) from baseline to week 16
- change in patient global (VAS) from baseline to week 16
- change in swollen joint count (SJC) from baseline to week 16
- change in tender joint count (TJC) from baseline to week 16
- change in number of tophi from baseline to week 16
- change in 36-Item Short Form Health Survey SF-36: Mental Component Scale (MCS) from baseline to week 16
- change in 36-Item Short Form Health Survey SF-36: Physical Component Scale (PCS) from baseline to week 16.

Section 3: Study Methods

Trial design

The study was designed as a 16 (8+8) week pragmatic proof-of-concept randomized, non-blinded, parallel-group trial. Treatment allocation was a 1:1 ratio. Patients were randomized to either 16 (8+8) weeks of low-energy diet (LED; 3.4 MJ/day; i.e., the Intensive Diet [ID] group) *OR* a corresponding 16-week with guidance on how to live with conventional hypo-energetic, high protein diet (app. 5 MJ/day) defined as a control group (i.e., conventional diet [CD] group).

Randomization

After baseline measurements, the participants were randomized to either Intensive Diet (ID) or Conventional Diet (CD) group. A computer-generated randomization sequence was produced, before any participants were enrolled, allocating participants in permuted blocks of 2 to 4 to the ID or the CD group (1:1). The randomization sequence was prepared using SAS Proc Plan; after the list was generated it was concealed in a password-protected computer file only accessible by the data manager. Randomization was stratified according to sex (M vs F), baseline obesity class (<40 vs. ≥ 40 kg/m^2), and SU level (< 6 vs. ≥6 mg/dL). These eight mutually independent randomization sequences (each including 60 "virtual patients") was entered into the eCRF by the data manager (CCH).

Power and sample size

Using SAS Power and Sample Size (Copyright © 2013 by SAS Institute Inc., Cary, NC, USA) it was calculated assuming that the standard deviation (SD) of weight change at week 16 would be 6.0 kg[29], that, 60 patients (30 in each group) would provide 89% confidence (power=0.888) to detect a clinically relevant 5 kg difference (p=0.05, two-sided) in mean bodyweight change between individuals allocated to intensive or conventional diet. If a drop-out rate of up to 20% (i.e., 6 patients in each group) is assumed, the trial will still have an acceptable power (>0.80) to detect a 5 kg difference between the groups.

Among the key secondary outcome measures is the mean change in SU at the final visit: Assuming a common SD of 1.6 mg/dL[30], a total sample size of 60 gout patients (randomized 1:1) will have a sufficient statistical power (81.5%) to detect a mean difference of 1.2 mg/dL[30]. Patient-Reported Outcome Measures (PROMs; e.g. VAS-Pain and VAS-fatigue): With 60 patients in total, the trial will have sufficient power to detect a statistically significant effect size (i.e. standardized mean difference [SMD]) corresponding to a large clinical effect (SMD=0.8; power=86.1%).

Framework

The trial aims to explore if an intensive diet is superior to a conventional diet regarding weight loss in a group of obese gouty arthritis patients.

Timing of final analysis

Final analysis is done after all patients have been included and finished the trial (after last-patient last-visit), and after full approval of this SAP by the investigators.

Timing of outcome assessments

The schedule of study procedures included is given in the table below.

Protocol schedule of forms and procedures				
VARIABLE	**Screening (approx. -2 wks)**	**Baseline (0 wks)**	**Intermediate (8 wks)**	**Endpoint (16 wks)**
Secretariat:				
Information Motivational appraisal Eligibility criteria/Screening (phone)	X			
Informed consent		X		
Demographics and clinical features:				
Age, years		X		
Male, y/n		X		
Ethnicity, n (%)		X		
Duration of gout, years		X		
Height, cm		X		
Body mass index, kg/m^2		X	(X)	(X)
Flares* in the preceding year, count		X		
Presence of palpable tophi, y/n		X	X	X
Comorbidities:				
History of kidney stones, y/n		X		
History of gall stones, y/n		X		
Cardio Vascular Disease, y/n		X		
Diabetes, y/n		X		
Hypertension, y/n		X		
Hyperlipidaemia, y/n		X		
Urate Lowering therapy:				
Allopurinol, y/n		X		
Febuxostat y/n		X		
Probenecid y/n		X		
Benzbromarone, y/n		X		
Anti-inflammatory prophylaxis:				
NSAIDs, y/n		X		
Prednisone, y/n		X		
Colchicine y/n		X		
Concurrent medication:				
Diuretics y/n		X		
Aspirin y/n		X		
Antihypertensive medication y/n		X		

Lipid lowering agents y/n		X		
Diabetes medication y/n		X		
Blood tests (lab. work):†				
Creatinine, mg/dL		X	X	X
eGFR, mL/min/1.73m^2		X	X	X
Serum urate, mg/dL		X	X	X
Physical examination (Nurse):				
Flares* in the last 8 weeks, count		X	X	X
Body weight, kg		X	X	X
Touch screen (PROMs):				
SF-36 health survey, score		X	X	X
Activity limitation (HAQ), score		X	X	X
Pain (VAS), mm		X	X	X
Patient global (VAS), mm		X	X	X
Fatigue (VAS), mm		X	X	X
Physical examination (MD):				
ACR/EULAR gout classification		X		
Gout according to expert opinion		X		
Swollen joint count, 0-66		X	X	X
Tender joint count, 0-68		X	X	X
Palpable tophi count		X	X	X
Randomisation (after confirming written informed consent)		X		
Harms and adverse events‡ (AEs):				
Withdrawal, y/n			X	X
Withdrawal due to AEs, y/n			X	X
Number of serious adverse events, count			X	X
Death, y/n			X	X

Section 4: Statistical Principles

Confidence intervals and P values

All analyses will be analyzed and reported as two-sided, done at a 5% significance level. Statistical tests will be conducted between the intensive weight loss and control group for the pre-defined primary and key secondary endpoints in a hierarchical manner. Thus gatekeeping procedure using serial testing will be applied to adjust for multiplicity among the key secondary outcomes[31]. Formal statistical testing will be performed, in a prespecified sequence, as presented below, until one of the key secondary endpoints in the hierarchy fail to be statistically significant at α=0.05. To limit the risk of type 1 errors we have selected only four endpoints to test - the primary endpoint and three key secondary endpoints. This procedure will preserve the "Family Wise Error Rate" of the

multiple analyses[32]. The analyses will be performed in sequence until one of the analyses has failed to show the significant difference or all analyses have been completed at a significance level of 0.05. The sequence of the analyses for the selected secondary efficacy endpoints are listed as: (1) Change in body weight; (2) Change in serum urate; (3) Change in VAS Fatigue. (4) Change in VAS Pain.

Analysis populations

Randomized trials are designed to address causal questions about options for care and thereby guide decisions by patients, clinicians, and other stakeholders. Thus, a rigorous trial should be analyzed according to the intention-to-treat principle, which require that patients assigned to a treatment strategy are kept in that group during the analysis, even if they deviate from their assigned treatment strategy after randomization. Primary analyses will be done on a modified ITT population, which include all randomized individuals who had the respective variable assessed at baseline.

Section 5: Trial Population

Screening

The number of individuals that have been screened for potential participation will be presented in the flow diagram (see draft figure 1 below).

Eligibility

Inclusion criteria: Participants will be included if they are above 18 years AND have a Body Mass Index (BMI) of at least 30 kg/m^2 AND per expert opinion have gout AND meet the 2015 American College of Rheumatology/EULAR gout classification criteria[33], and with SU $\geq$5 mg/dL.

Exclusion criteria: Pregnant or breastfeeding. A history or suspicion of drug abuse within the past 5 years. Active muscle disease, cancer, previous kidney disease, and/or fatty liver. An estimated creatinine clearance <30 mL/min calculated by the Cockcroft-Gault formula using ideal body weight. An investigational therapy within 8 weeks or 5 half-lives (whichever is longer) prior to the screening visit. Any other medical or psychological condition which, in the opinion of the investigator and/or medical monitor, might create undue risk to the patient or interfere with the

patient's ability to comply with the protocol requirements, or to complete the study. The number of included participants will be presented in the flow diagram (see figure 1).

Baseline patient characteristics

Patients will be described with respect to all variables shown in Table 1 in 'Proposed outline of tables and figures' below, separately for the two randomized groups. Data from the baseline visit will be used.

Section 6: Analysis

Outcome definitions

Primary Outcome:

Change in bodyweight (measured in kilograms) from baseline to the week 16 visit in the intention-to-treat (ITT) population.

Key Secondary Outcomes:

Change in SU at the final visit (16 weeks); Change in fatigue (VAS), and change in pain from their gout at their final visit (VAS).

Other Secondary Outcomes:

The proportion of participants reaching and maintaining target SU levels, defined as 8 weeks and 16 week visits with SU<6 mg/dL, respectively; the percentage reduction in SU at final visit (week 16); the proportion of individuals with any gout flare in the first-, and last 8 weeks following randomization, respectively; the number of gout flares during the trial period for each patient; functional status (HAQ); patient global (VAS); swollen joint count (SJC); tender joint count (TJC); change in number of tophi from baseline; and 36-Item Short Form Health Survey (SF-36: MCS and PCS apply).

Analysis methods

For the primary and key secondary outcomes, we will use analysis of covariance (ANCOVA) modelled using repeated-measures mixed linear model analysis. Statistical tests inferring from P-values will be performed in sequence until one of the analyses has failed to show the significant difference or all analyses have been completed at a significance level of 0.05. The sequence of the analyses for the selected secondary efficacy endpoints are listed as: (1) Change in body weight; (2) Change in serum urate; (3) Change in VAS Fatigue. (4) Change in VAS Pain. The statistical model will include diet group (ID/CD) and time (in weeks) as fixed effects, and the interaction between time and diet group, with the respective variable (e.g. body weight at baseline) as covariate. Furthermore, the possible impact of the factors used for the stratified randomization will be explored, i.e. sex (M/ F), obesity class (<40/≥40 kg/m2), and SU level (< 6/≥6 mg/dL) but will not be considered part of the primary model. We aim to assess whether data provide evidence of superiority of ID to CD group (primary objective). Thus, the null hypothesis is no difference

between treatments at endpoint (week 16). Response variables and adverse events (binary outcomes) will be analyzed by comparing the proportions responding in each group with the Risk Difference (and 95% CI's), with no further adjustments for covariates.

Missing data

Missing data will be handled implicitly by the mixed model for the main analyses (Table 2). Incomplete outcome data, for example, caused by patients missing some visits or dropping out of the study, are common in longitudinal studies. Mixed models assume that the missingness is independent of unobserved measurements, but dependent on the observed measurements[34]. This assumption is called "*Missing At Random*" (MAR) and is often reasonable[35]: Using mixed models, valid estimates of treatment effects will be obtained even when the missing values are not completely random ("*Missing Completely At Random*", [MCAR]) and additional methods for handling missing data, such as multiple imputation, are generally not required[34].

Missing data have until recently, seriously compromised inferences from clinical trials[35]. For example, editorials in the New England Journal of Medicine have noted how missing data have limited the ability to draw definitive conclusions from weight-loss trials[36]. Analyses that are performed with methods such as repeated measures mixed models often assume that missing data are missing at random (MAR), and such an assumption often makes sense for the primary analyses. However, the observed data can never verify whether this assumption is correct. Therefore, we will assess robustness by using sensitivity analyses, noting that explicit use and reporting of sensitivity analyses is a novel area in trial research; i.e. the interpretation of the collective results from a sensitivity analysis when some of the analyses are in opposition to the primary analysis are not without controversies. However, we will assess the robustness of inferences (from our primary analyses) about treatment effects to various missing-data assumptions by conducting sensitivity analyses that relates inferences to one or more parameters that capture departures from the primary missing data assumption.

Sensitivity analyses should be easy to interpret by clinicians. We will apply the framework suggested by White et al, published in the British Medical Journal (2011)[37] for intention to treat analysis that depends on making plausible assumptions about the missing data and including all participants in sensitivity analyses:

1. We did our best to follow up all randomized participants, even if they withdrew from their allocated treatment (i.e. real data is better than statistical imputation strategies).
2. We will perform a main analysis of all observed data that are valid under a plausible assumption about the missing data by using repeated measures mixed linear models (valid assuming that data is '*Missing At Random*'); See Table 2.
3. We will perform sensitivity analyses to explore the effect of departures from the assumption made in the main analysis; see SAP-Appendix Tables 1 and 2.

4. We will account for all randomized participants, also in the sensitivity analyses:
    - We will apply a "non-responder imputation techniques" for the missing data (using BOCF) in the analyses provided in SAP-Appendix Table 1 (potentially valid even if data is '*Not Missing At Random*' [NMAR]).
    - We will apply a naïve approach where we only perform our analyses on the data set where participants with missing data is excluded; i.e. participants with complete data for all of the four outcomes while still respecting the original treatment allocation (i.e. valid assuming data is Missing Completely at Random; MCAR), and using simple two-sample t-tests; see SAP-Appendix Tables 2.

If the treatment effect is qualitatively maintained for the range of offsets that are clinically plausible, then the findings will be considered robust. Extensions apply the offsets to means adjusted for available covariates (e.g. stratifying factors).

Harms and adverse events

The number (and percentage) of patients experiencing any AE/SAE will be presented for each treatment group including gout flares.

Statistical software

The analysis will be carried out using SAS Studio and R version 3.6.0 (or newer).

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Proposed outline of tables and figures:

Figure 1: CONSORT flow diagram

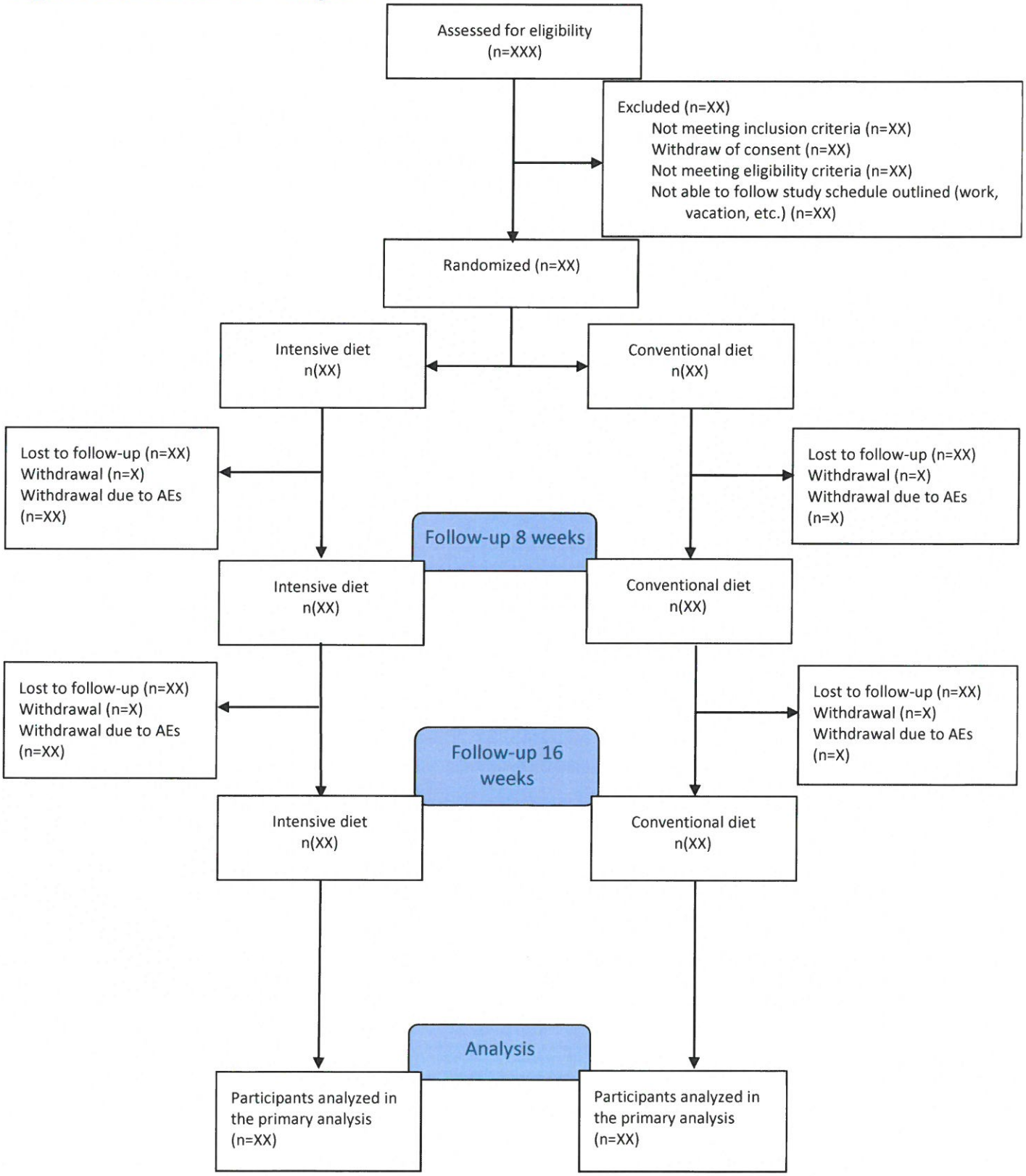


Table 1: Baseline characteristics

Baseline characteristics			
Variables	**ID (n=XX)**	**CD (n=XX)**	**Total (n=XXX)**
Age, years			
Male sex, n(%)			
Ethnicity (Caucasian), n(%)	100%	100%	100%
Body weight, kg			
BMI, m/kg^2			
BMI ≥ 40 kg/m^2, n(%)			
Duration of gout, years			
Serum urate, mg/dL			
Serum urate ≥ 6 mg/L, n(%)			
Presence of palpable tophi, n(%)			
Comorbidity:			
Kidney stones, n(%)			
Gall stones, n(%)			
Cardiovascular disease, n(%)			
Diabetes, n(%)			
Hypertension, n(%)			
Hyperlipidemia, n(%)			
Any urate lowering therapy, n(%)			
Any anti-inflammatory medication:			
Colchicine, n(%)			
NSAID, n(%)			
Prednisone, n(%)			
Outcome Measures:			
VAS fatigue, 0-100 mm			
VAS pain gout, 0-100 mm			
VAS pain global, 0-100 mm			
HAQ			
Swollen joint count			
Tender joint count			

Palpable tophi,			
SF 36 MCS, 0-100 points			
SF 36 PCS, 0-100 points			

Values are means (SD), unless otherwise stated. Abbreviations: ID – Intensive diet, CD – Conventional diet.

Figure 2A: Weight in kg among the two groups

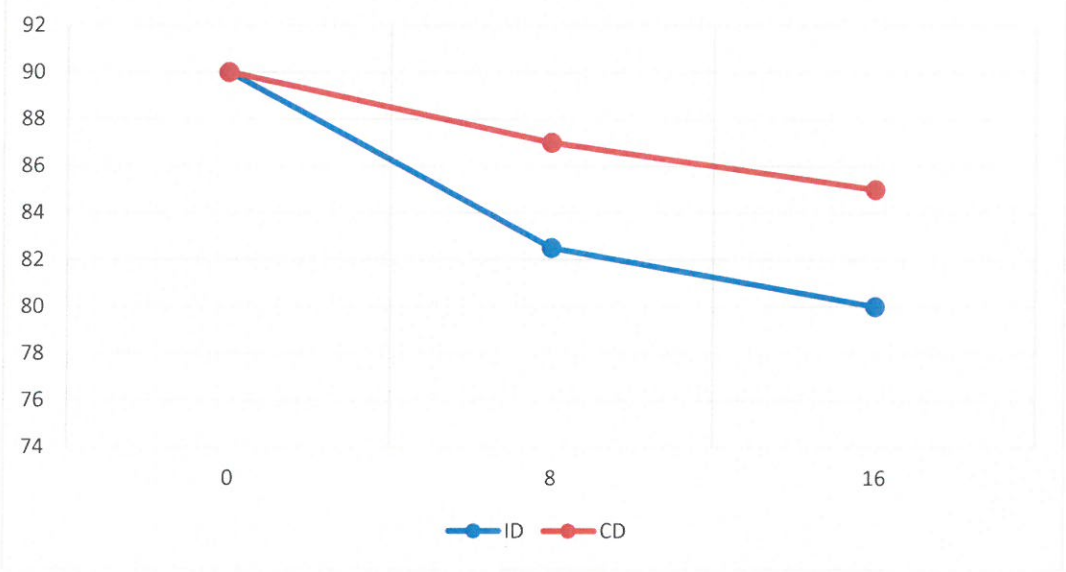
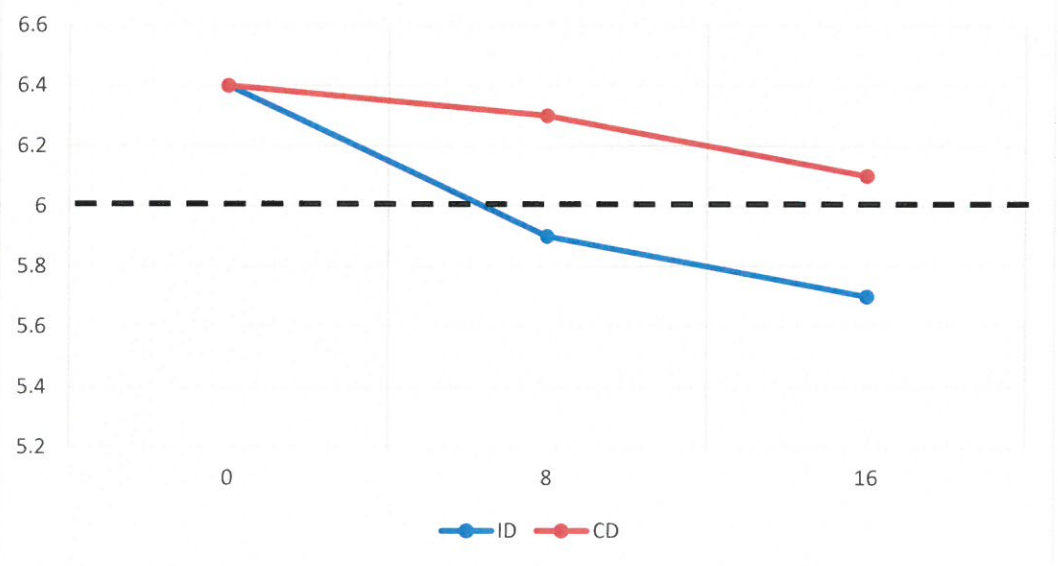


Figure 2B: Serum urate in mg/dL among the two groups (ABS)



From the Linear Mixed Models, the Least Squares Means estimates will be based on our primary statistical model(s). Values will be illustrated as the absolute value (i.e. not change from baseline which will be used for Table 2). Error Bars will – in the final figure - illustrate the standard error for the least squares means. The dashed line illustrates the treatment goal for non-tophous gout 6mg/dL. Abbreviations: ID – intensive diet, CD – conventional diet.

Table 2: Changes in primary and secondary endpoints

	Change from baseline[1,2]				
	Outcome	**ID (n=XX)**	**CD (n=XX)**	**Difference (95%CI)**	**P-value**
Primary outcome	Weight loss, kg				
Key secondary outcomes	Serum urate, mg/dL				
	VAS fatigue				
	VAS pain gout				
Other secondary outcomes	On treatment target, n(%)*				n.a.
	Serum urate reduction, %				n.a.
	VAS patient global				n.a.
	HAQ				n.a.
	Swollen joint count				n.a.
	Tender joint count				n.a.
	Palpable tophi				n.a.
	SF-36 MCS				n.a.
	SF-36 PCS				n.a.

Abbreviations: ID - Intensive diet, CD – conventional diet.

1: Continuous outcome estimates will be derived from the repeated measures linear mixed models where missing data in the ITT population is handled implicitly; the inference will be provided as the difference between least squares means with 95 CI's around them.

2: Dichotomous outcomes will be reported directly as observed (no imputations); the inference will be provided (unadjusted as the difference between proportions, i.e. Risk Difference, with 95% confidence interval).

*Defined as having a serum urate < 6.0 mg/dL at both week 8 *AND* week 16

Table 3: Adverse events and harms

Event	ID (n=XX)	CD (n=XX)	Difference (95%CI)
Self-reported flare, 0-16 weeks			
First 8 weeks (0-8)			
Last 8 weeks (8-16)			
Other			
Serious Adverse Events, 0-16 weeks			
Death			

Abbreviations: ID - Intensive diet, CD – conventional diet.

These dichotomous adverse outcomes will be reported directly as observed (no imputations) with number and percentages; the inference will be provided (unadjusted) as difference between proportions (i.e. Risk Difference, with 95% confidence interval).

Prespecified Appendices

***SAP-Appendix Table* 1:** Changes in primary and key secondary endpoints (using non-responder imputation)

		Change from baseline[1]			
	Outcome	**ID (n=XX)**	**CD (n=XX)**	**Difference (95%CI)**	**P-value**
Primary outcome	Weight loss, kg				
Key secondary outcomes	Serum urate, mg/dL				
	VAS fatigue				
	VAS pain gout				

Values are least squares means (SE), unless otherwise stated. Abbreviations: ID – intensive diet, CD – conventional diet.

1: Continuous outcome estimates will be derived from the repeated measures linear mixed models where missing data in the ITT population is handled explicitly with a non-responder imputation (i.e. baseline observation carried forward; indicative of a possible NMAR issue); the inference will be provided as the difference between least squares means with 95% CI's around them.

SAP-Appendix Table **2:** Changes in primary and key secondary endpoints (using 2-sample t-tests)

		Change from baseline[1]			
	Outcome	**ID (n=XX)**	**CD (n=XX)**	**Difference (95%CI)**	**P-value**
Primary outcome	Weight loss, kg				
Key secondary outcomes	Serum urate, mg/dL				
	VAS fatigue				
	VAS pain gout				

Values are means (SD). Abbreviations: ID – intensive diet, CD – conventional diet.

1: Continuous outcomes estimates will be derived from descriptive statistics and 2-sample t-tests (change from baseline at 16 weeks) where missing data is handled explicitly by excluding participants with missing data for any of the four outcomes while still respecting the original treatment allocation (i.e. valid assuming data is missing completely at random); the inference will be provided as the difference group means with 95% CI's around them.

SAP-Appendix Table **3:** Changes in primary and key secondary endpoints (adjusted for the three stratifying factors)*

Change from baseline[1]

	Outcome	ID (n=XX)	CD (n=XX)	Difference (95%CI)	P-value
Primary outcome	Weight loss, kg				
Key secondary outcomes	Serum urate, mg/dL				
	VAS fatigue				
	VAS pain gout				

Values are least squares means (SE), unless otherwise stated. Abbreviations: ID – intensive diet, CD – conventional diet.

*Based on the same statistical model as the primary analyses (Table 2); adding three further covariates corresponding to the stratified analysis.

1: Continuous outcome estimates will be derived from the repeated measures linear mixed models where missing data in the ITT population is handled explicitly with a non-responder imputation (i.e. baseline observation carried forward); the inference will be provided as the difference between least squares means with 95% CI's around them.