# Statistical Analysis Plan:

# A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Pragmatic Clinical Trial to Evaluate the Effectiveness of Low Dose Oral Methotrexate in Patients with Pediatric Crohn's Disease Initiating Anti-TNF Therapy

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**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER PRAGMATIC CLINICAL TRIAL TO EVALUATE THE EFFECTIVENESS OF LOW DOSE ORAL METHOTREXATE IN PATIENTS WITH PEDIATRIC CROHN'S DISEASE INITIATING ANTI-TNF THERAPY**

# DATA ANALYSIS PLAN

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# 1 STUDY DESIGN

We will conduct a placebo-controlled, double blind, pragmatic, multi-site randomized clinical trial to determine whether, in children with Crohn's disease (CD) initiating anti-TNF biological therapy, low-dose oral MTX is more effective than placebo in the induction and subsequent maintenance of steroid-free remission. We will use randomization by constrained block[1] within each site, stratified by anti-TNF agent used (infliximab or adalimumab), to ensure balanced treatment allocation within individual sites.

Nested within this pragmatic clinical trial, we will conduct a, cluster randomized controlled trial to determine whether, in parents (of children with CD) or patients $\geq$ 18 years old being approached for trial participation, a pre-consent discussion enhanced with decision aids is more effective than the standard pre-consent discussion in transferring knowledge to parents/patients related to trial participation. Sites will be randomly assigned 1:1 to the intervention or control group before recruitment begins at each site. We will use a covariate-constrained randomization procedure[2] to ensure that the intervention and control sites are balanced at baseline with respect to approximate number of patients with CD started on an anti-TNF agent in the past year. This is important to ensure that a similar number of patients are approached for trial participation at intervention and control sites. Randomization will occur at the site level so that all providers and research staff at a site will be assigned to the same randomization condition to increase the feasibility of protocol implementation and decrease risk of contamination across study arms. A cluster randomized trial is necessary to control for measured and unmeasured confounders, as well as potential biases that could impact the assessment of study outcomes

# 2 STUDY ENDPOINTS

## *2.1 Primary Endpoints*

Primary Outcome - Induction and maintenance of steroid-free remission for 104 weeks. This will be analyzed as time to first *treatment failure*, as defined by occurrence of any of the following:

- Failure to achieve remission (SPCDAI < 15) by the week 26 visit. This endpoint will be assessed using the Week 26 visit form or the form from the first visit after week 26 if the Week 26 visit is missed.
- If initiating the study on steroids, failure to complete a steroid taper by week 16. This endpoint will be assessed using the first Concomitant Medications form filled out at or after week 16.
- SPCDAI $\geq$ 15 (active disease) at two or more consecutive visits beyond the week 26 visit. This endpoint will be assessed using all visit forms after the Week 26 visit.
- Hospitalization for active IBD or abdominal surgery after week 25. This endpoint will be assessed by using the Registry Hospitalization form.
- Use of oral prednisone or prednisolone, enteral release budesonide, or intravenous (IV) methylprednisolone for a period of over 10 weeks cumulatively, beyond week 16. Note, this does not include use of steroid as a premedication for anti-TNF administration or steroids

used for conditions other than CD (e.g. asthma, poison ivy, etc.). This endpoint will be assessed using the Concomitant Medications form.

- Discontinuation of the anti-TNF agent and/or study drug for lack of effectiveness or toxicity. This endpoint will be assessed using the Concomitant Medications form and the Methotrexate/Placebo Dose Changes form.

Discontinuation of anti-TNF in the setting of treatment de-escalation will not be considered as a treatment failure. Neither will discontinuation of the anti-TNF or study medication for non-medical reasons (i.e. desire to switch to an alternative therapy).

### *2.2 Secondary Endpoints*

There are three secondary study endpoints:

1. Mean Patient Reported Outcome Measurement and Information System (PROMIS) Pain Interference T score by treatment arm. We will compare the mean of PROMIS Pain Interference T scores at week 52 and week 104 between the treatment groups.

2. Mean PROMIS Fatigue T score by treatment arm. We will compare the mean of PROMIS Fatigue T scores at week 52 and week 104 between the treatment groups.

3. Proportion of patients with positive anti-TNF antibody status based on the sample collected in the second year (week 91). If a sample is not collected in the second year, the sample collected in the first year will be used (week 14).

### *2.3 Tertiary Endpoints*

Indirect and direct markers of disease activity and mucosal inflammation and healing. Objective and firm endpoints are increasingly recognized as important outcomes of explanatory trials in CD, including clinical efficacy studies designed for FDA approval. These include routine laboratory assessments including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), albumin, and hemoglobin.

There are many additional tests for which there is ongoing debate regarding routine clinical use due to their high cost and/or invasive nature [calprotectin (biomarker of intestinal inflammation) and endoscopy)]. Given the pragmatic nature of this trial, we will not mandate the use of such tests by study protocol. Rather, we will collect these test results if/when they are performed in the context of each patient's routine clinical care. We will educate clinicians on one endoscopic scoring system commonly utilized to assess disease activity in clinical studies, the Simple Endoscopic Score for Crohn's Disease (SES-CD), so that they may more accurately report their endoscopic findings. As we anticipate that routine use of such testing to assess mucosal healing will increase over the next several years, this will minimize the potential for differential testing based on patient clinical status.

Change in anti-TNF dose or interval. The anti-TNF dose may be changed at the discretion of the treating provider. Changes in anti-TNF dosing will be recorded, as will the reason for these changes, and this will be analyzed as pre-specified endpoints.

Other endpoints to be analyzed include anti-TNF trough levels, induction of remission, maintenance of remission, and height velocity Z scores. We will assess induction of remission through the week 26 visit (window 22-30 weeks) and maintenance of remission beginning after the week 26 visit.

### *2.4 Safety Endpoints*

The major safety concerns for PCD patients undergoing treatment with anti-TNF biologics (with or without combination therapy) include the risk of opportunistic infections and malignancy. Safety concerns with MTX include bone marrow suppression, hepatotoxicity, nausea, and hair loss. Although this trial is designed primarily for CER rather than safety, we will monitor AEs regularly and we will work with a Data Safety Monitoring Board (DSMB) to detect any adverse safety signals. Many of the safety concerns, including malignancy, are primarily long-term considerations that are beyond the duration of most clinical trials, and are better assessed from registries involving thousands of patients. However, a key strength of conducting this study in the context of ICN is that long-term safety data will continue to be collected by the network and accumulate following the conclusion of the funded trial itself. Hence, this trial will lay the groundwork for long-term safety studies.

### *2.5 Endpoints for Trial of Enhanced vs. Standard Pre-Consent Discussion*

The primary outcome is the percentage correct on parent/patient knowledge items related to trial participation. The secondary outcome is the percentage of parents/patients who agree to enroll in the pragmatic clinical trial.

## 3 SAMPLE SIZE

Our sample size calculation is based upon our primary aim and outcome—induction and maintenance of steroid free remission. We estimate our needed sample size on the following assumptions:

1. *Induction and maintenance of steroid-free clinical remission through week 104 will occur in 50% of the monotherapy group*. This is based on the two adult trials of anti-TNF combination versus monotherapy in CD. In these trials, treatment success rates in the monotherapy group at the end of year 1 were 40% and 56%. We anticipate that treatment success will diminish somewhat over the 2$^{nd}$ year of follow-up. Therefore, the actual rates of treatment success in our trial may be somewhat less than 50%. However, as 50% is among the possible values, we used it in our power calculations. This is a conservative assumption, as any deviations from this will result in greater statistical power.

2. *True difference between the two treatment arms will be 15% or more.* We believe that a 15% difference is the minimum clinically important difference, as smaller effects will not warrant the

incremental toxicity of combination therapy. The two adult studies[25 26] were powered only to detect a 20% and 25% difference; however, we believe that a smaller difference would still be clinically meaningful. We think a 15% differences is a reasonable estimate of the treatment effect. In the SONIC study (combination therapy with 6MP), the observed difference at 1 year was 16%[26], and we anticipate a greater difference over an additional year of follow-up. Although no difference in treatment arms was observed in the COMMIT study (combination therapy with MTX), this may have resulted from a number of methodological limitations that have been addressed by our trial design.

3. *We anticipate a loss to follow up of no more than 17%.* Based on data from 2013, loss to follow up in the ICN network is approximately 6% per year, or 12% over a two-year trial. For this trial, we assume an additional 5% loss to follow-up to account for withdraws of consent or other reasons for study drop-out.

Based on the assumptions above, 146 treatment failures are required to achieve the power of 80% with two-sided 0.05 level test. Accounting for staggered entry and loss to follow up, we anticipate we will need to recruit a total of 425 patients to observe required number of treatment failures. These power calculations are based on the assumption that time to failure is exponentially distributed.

## 4 PLANNED INTERIM ANALYSIS

We will perform an interim analysis for efficacy using O'Brien-Fleming boundary after 73 patients experience a treatment failure (half of the required treatment failures). The null hypothesis will be rejected if the p-value is less than 0.005. The final analysis will be done at 0.048 $\alpha$-level to ensure that the overall $\alpha$-level does not exceed 0.05.

We will also perform and interim analysis for efficacy for the nested trial of enhanced vs. standard pre-consent discussion. This will occur after the first 200 subjects have accrued ($n$ = 100 each arm).

## 5 STATISTICAL ANALYSIS PLAN

### *5.1 Statistical analysis*

Descriptive Statistics. SAS software (SAS Institute, Cary NC) will be used to perform all analyses. We will compute the treatment-arm-specific proportions and exact 95% confidence intervals of patients achieving each primary and secondary outcome of interest. We will describe and summarize the bivariate distributions of patient characteristics (age, sex, duration of disease, previous therapies, disease extent, disease severity, laboratory tests) within treatment arms. We will compute medians, interquartile ranges, means and standard errors of continuous variables. Categorical variables will be summarized using proportions in each level. We will compare distributions across treatment arms as follows: (1) for categorical variables, Fisher's exact chi-square tests of association in 2-by-X tables, or (2) for continuous variables, either Student's t-tests of differences in means (for normally distributed variables), or Wilcoxon rank-sum tests for

non-normally distributed variables. Because any imbalance in the two randomized groups is by definition a chance occurrence, these descriptive analyses will be used to highlight potential areas of substantial unbalance between the study arms and to inform adjusted analyses of treatment effect.

Primary analyses. The primary endpoint is time to treatment failure. Patients who fail to enter remission will be considered as a treatment failure at the visit at or just prior to week 26. To compare the distribution of time to treatment failure in the two arms we will compute stratified log-rank test stratified by anti-TNF agent prescribed (infliximab and adalimumab).

Additional analysis of the primary endpoint. We will also perform the un-stratified log-rank test. Cox model with treatment (MTX versus placebo), site, anti-TNF agent prescribed (infliximab and adalimumab) and important covariates (see Potential confounders below) will be considered. Since some sites will recruit a small number of patients, we will combine sites based on the geographic location to have a total of 6-8 site clusters.

The Kaplan Meier method will be used to estimate the probabilities of treatment failure, induction rates, and the maintenance of steroid free remission rates at various time points (week 26, 52, 104) in the two groups (MTX versus placebo). Survival curves will be presented for time to induction and time to relapse. We will also evaluate the probability of treatment failure through week 104.

Analysis of the secondary endpoints. The three secondary endpoints will be tested using the Bonferroni multiple comparison procedure. Since the three secondary endpoints are likely to be positively correlated, Bonferroni is a conservative approach to controlling for multiplicity here. The first secondary endpoint is the average of PROMIS Pain Interference T scores at weeks 52 and 104. We first compare the average of PROMIS Pain Interference T scores at week 52 and week 104 between the treatment groups. If this comparison is significant at 0.05/3 level, we will compare the treatment groups based on PROMIS Pain Interference T score at week 52 and separately based on week 104 at 0.05/3 level each. To perform this analysis, the means and the variability of the PROMIS scores at 52 and 104 weeks will be estimated by fitting mixed model for repeated measures (MMRM) to PROMIS scores at all available time points adjusted for important covariates. The second secondary endpoint is the average of PROMIS Fatigue T scores at weeks 52 and 104. We will compare the averages of PROMIS Fatigue T scores at week 52 and week 104 between the treatment groups. If this comparison is significant at 0.05/3 level, we will compare the treatment groups based on Fatigue T score at week 52 and separately based on week 104 at 0.05/3 level each. To perform this analysis, the means and the variability of the PROMIS scores at 52 and 104 weeks will be estimated by fitting MMRM to PROMIS scores at all available time points adjusted for important covariates. The third secondary analysis is the comparison of proportions of patients with positive anti-TNF antibody status based on the sample collected in the second year (week 91). If a sample is not collected in the second year, the sample collected in the first year will be used (week 14). The proportions in the two groups (MTX versus placebo) will be compared using logistic regression with adjustment for important covariates using 0.05/3 significance level.

Analysis of additional endpoints. Additional pre-specified endpoints, listed below, will be analyzed using appropriate statistical methods: Wilcoxon rank-sum test to compare mean anti-

TNF levels and dose and chi-squared test to compare proportions. Parameter estimates for PROs will be obtained from the MMRM.

1. Mean anti-TNF levels form the specimen collected during 2nd year of follow up.
2. Proportion of patients with normal ESR and mean ESR at various time points (week 26, 52, 104).
3. Proportion of patients with normal CRP at various time points (week 26, 52, 104).
4. Proportion of patients at various time points (week 26, 52,104) with the following (on anti-TNF, requiring dose escalation of anti-TNF, without hospitalization, without surgery, without any steroid for IBD, without steroid for IBD > 10 weeks cumulatively (beyond week 16).
5. Proportion of patients achieving steroid free remission by the week 26 visit (+/- on original anti TNF and study drug).
6. Proportion of patients in steroid free remission at week 104 (+/- on original anti TNF and study drug).
7. Proportion of patients with height velocity Z score at week 104 that is better -1.
8. Proportion of patients with normal calprotectin (< 150) at week 104 (select measurement between week 52 and 104, closest to 104).
9. Proportion of patients with endoscopic healing (defined by SES-CD and/or PGA) at week 104 (select measurement between week 52 and 104, closest to 104).
10. PROMIS Positive Affect, and IBD Symptom PRO T score (continuous variable, mean in general population = 50, SD = 10) at week 26, 52, 104.
11. PROMIS Fatigue and Pain Interference at week 26.
12. Mean anti-TNF dose (per kg) at week 26, 52, 104 in the two groups.

Potential confounders. Adjusted models will consider the following potential confounders, as assessed at baseline: the anti-TNF agent used, SPCDAI score, current or prior use of prednisone and other steroid medications, prior use of MTX, prior use of 6 mercaptopurine or azathioprine, time from diagnosis (< 2 or ≥ 2 years), elevation of baseline CRP or ESR as a measure of inflammation and disease activity, age (< or ≥ 12 years), gender, and race.

Multiplicity adjustment. A multiple comparison procedure that preserves the type I error rate for the study is to perform the test of the primary endpoint using the primary analysis specified in the protocol. The primary test is declared to be significant if its p-value is less than 0.05. A comparison based on each of the three secondary endpoints is declared to be significant if this comparison is significant at 0.05/3 level and if the primary comparison is significant at 0.05 level. We will ascertain whether or not the analysis of primary and secondary endpoints is significant based on this strict procedure that preservers the study's overall type I error rate at 0.05.

Pre-specified subgroup analyses. We will perform analysis in the following subgroups: type of anti-TNF, time from diagnosis (< 2 or ≥ 2 years), baseline disease activity (SPCDAI score ≥ 30) at enrollment, and elevation of baseline CRP or ESR as covariates. Other covariates to consider are gender, age (< or ≥ 12 years), race/ethnicity, CD subtype based on the Paris Classification,

and other relevant clinical/phenotypic characteristics (i.e. presence of perianal lesions). Additional subgroup analyses based on anti-TNF starting dose will be performed, if applicable.

An additional subgroup analysis will be based upon whether the anti-TNF dose was prescribed according to a traditional weight-based dosing model or whether the dose was adjusted based upon measurement of trough levels. We will ascertain the use of level-based dose adjustments and will evaluate whether this practice results in higher induction/maintenance of remission or is an effect modifier of the combination versus monotherapy comparison.

For each subgroup analysis, we will: 1) test for an interaction of treatment by subgroup, 2) estimate the treatment effects within each subgroup, and 3) use a graphical approach to display treatment effects within appropriate subgroups (i.e., meta-analysis forest plot). Although the study will not have adequate power for each of these subgroup analyses, estimating the effect size and precision will provide very useful hypothesis-generating data, even in the absence of statistical significance.

Missing data. Some components in the definition of the primary outcome might be imputed (see below) and, generally, missing covariates in our models will be imputed using multiple imputation.

Some components in the definition of the primary outcome - treatment failure- might not be available in some instances. The SPCDAI score is comprised of 6 separate components. If the composite score is greater than or equal to 15, and the provider confirms that the patient is not in remission, any missing SPCDAI components will not be imputed. The score will stand regardless of missing data, and the patient will be considered a treatment failure at the appropriate time points. If the composite score is less than 15 and two or less of the 6 components of the SPCDAI are missing at the visit, the missing data will be imputed based on the estimated joint distribution of the SPCDAI components using multiple imputation[3]. The composite score calculated via imputation of the missing components will be utilized to assess treatment failure. If the composite score is less than 15 and three or more of the 6 components of the SPCDAI are missing at the visit, the visit score will not be utilized to determine occurrence of treatment failure.

PROMIS scores will not be imputed using multiple imputation. We will investigate if the missingness of the PROMIS scores is related to the patient meeting the primary endpoint of the study. If missigness does not seem to be related to the primary endpoint, we will use MMRM to analyze the PROMIS scores, otherwise PROMIS scores will be analyzed at each time point separately.

Observational CER study of patients treated with thiopurine combination therapy. Some patients in the network will decline study participation and some will undergo treatment with combination therapy of anti-TNF and 6MP or azathioprine, either due to patient and/or provider preference. By conducting this trial within ICN, we will be able to perform an observational cohort study of these patients. Specifically, we will compare the baseline characteristics of trial participants with patients treated with anti-TNF + 6MP/azathioprine combination therapy. We will also be able to perform unadjusted and adjusted analyses comparing the two study arms with this 3rd observational arm.

Additional analysis of PROs. PROs include PROMIS domains, which are continuous measures, calibrated using a T-score metric to the US general population with a mean of 50 and standard deviation of 10. Minimal important differences (MIDs) for many PROMIS domains are in the range of 2 to 6. Our analysis plan will take advantage of the longitudinal nature of selected PROs, and the MMRM will be used for analysis. Groups will be compared over a given set of time points.

AEs and safety analyses. We will use descriptive statistics (e.g., proportions, 95% confidence intervals (CI)) to summarize physician reported AEs. We will also compare the following safety outcomes between the two treatment groups:

- elevated liver enzymes (> 2X upper limit of normal),
- Other hepatotocicity
- leukopenia (WBC < 3.0)
- Platelets < 100
- serious infections,
- malignancies,
- nausea,
- IBD related hospitalizations / surgeries from the registry

Interim analyses will be reviewed by the DSMB at regular intervals (see Protection of Human Subjects).

As required by clinicaltrials.gov, we will report ALL SAEs and any non-serious adverse events that occur at a frequency of >5% within any arm (these will be reported for each arm).

In addition to safety monitoring during the study period, we will also perform longer-term safety monitoring after the conclusion of the study, as data will continue to be collected on trial participants as part of routine clinical care in ICN.

### *5.2 Subject Population(s) for Analysis*

We will conduct an Intent to Treat Analysis. Any subject randomized into the study, regardless of whether they received study drug, will be included in the analyses.

### *5.3 Enhanced vs. Standard Pre-Consent Discussion*

We will compare these two groups on our primary outcome of the percentage correct on parent/patient knowledge items related to trial participation and the secondary outcome of the percentage of parents/patients who agree to enroll in the pragmatic clinical trial. Hierarchical linear models will account for the clustering of subjects within sites.

## 6 REFERENCES


1. Berger VW, Ivanova A, Knoll M. Minimizing predictability while retaining balance trough the use of less restrictive randomization procedures. Statistics in Medicine 2003; 22, 3017-3028.
2. Ivers NM, Halperin IJ, Barnsley J, et al. Allocation techniques for balance at baseline in cluster randomized trials: a methodological review. Trials 2012;13:120.
3. Rubin DB. Multiple imputation for nonresponse in surveys. Hoboken, N.J.;: Wiley-Interscience, 2004.

Table 1. Demographic and Baseline Characteristics of the Study Patients

| | Infliximab + MTX | Infliximab + Placebo | Adalimumab + methotrexate | Adalimumab + Placebo | All Anti-TNF + Methotrexate | All anti-TnF + Placebo |
|---|---|---|---|---|---|---|
| Patients randomized, n | | | | | | |
| Mean age, y | | | | | | |
| Male gender | | | | | | |
| White race, n (%) | | | | | | |
| Weight, kg | | | | | | |
| Ht, cm | | | | | | |
| Time since diagnosis, mo | | | | | | |
| Disease location, n (%)<br>Small bowel<br>Ileocoliits (small bowel and colon)<br>Colitis (colon)<br>Unknown | | | | | | |
| Upper GI involvement, (n (%) | | | | | | |
| Perianal involvement (%) | | | | | | |
| Prior azathioprine or mercaptopurine therapy, n (%) | | | | | | |
| Prior methotrexate, n (%) | | | | | | |
| Prednisone at randomization, n (%) | | | | | | |
| SPCDAI score at randomization, n (%) | | | | | | |
| Mean sed rate at randomization | | | | | | |
| ? elevated CRP at randomization, n (%) | | | | | | |
| Perianal disease at enrollment (n, (%) | | | | | | |
| History of perianal disease n (%) | | | | | | |

**Figure 1: Stnadard consort diagram**

**Figure 2: Kaplan-Meier estimates of time to treatment failure**

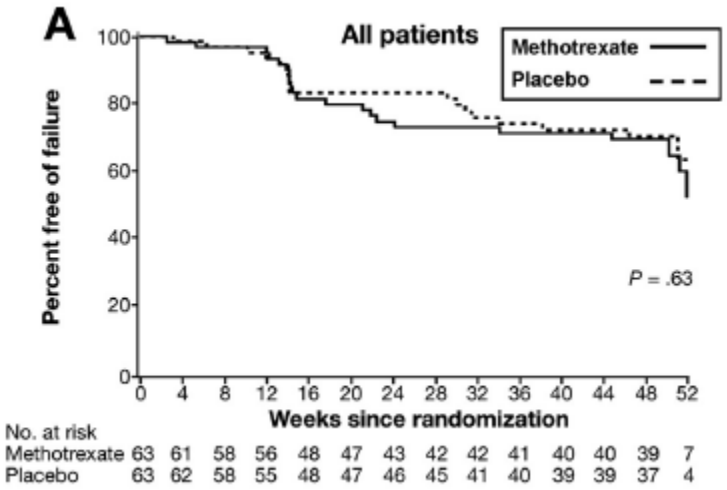

Table 2:
Rates of induction and steroid free remission at various timepoints

| | Infliximab + MTX | | Infliximab + Placebo | | Adalimumab + methotrexate | | Adalimumab + Placebo | | All anti-TnF + Placebo | | All anti-TnF + Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | | Mean (SD) | p | Mean (SD) | | Mean (SD) | p | Mean (SD) | | Mean (SD) | p |
| % successful induction of remission by week 26 | | | | | | | | | | | | |
| % maintanence of steorid free remission through week 52 | | | | | | | | | | | | |
| % maintanence of steroid free remission through week 104 | | | | | | | | | | | | |

Table 3 Patient Reported Outcome Measurement Information System Fatigue Score at Various Timepoints

| | Infliximab + MTX | | Infliximab + Placebo | | Adalimumab + methotrexate | | Adalimumab + Placebo | | All anti-TnF + Placebo | | All anti-TnF + Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mea | | Mea | p | Mea | | Mea | p | Mea | | Mea | p |

| | n (SD) | | n (SD) | | n (SD) | | n (SD) | | n (SD) | | n (SD) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Average of Week 52 and 104 | | | | | | | | | | | | |
| Screening | | | | | | | | | | | | |
| Week 15 | | | | | | | | | | | | |
| Week 26 | | | | | | | | | | | | |
| Week 52 | | | | | | | | | | | | |
| Week 104 | | | | | | | | | | | | |

Table 4: Anti TNF antibody status, level, and dose at last measurement

| | Infliximab + MTX | | Infliximab + Placebo | | Adalimumab + methotrexate | | Adalimumab + Placebo | | All anti-TnF + Placebo | | All anti-TnF + Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | | Mean (SD) | p | Mean (SD) | | Mean (SD) | p | Mean (SD) | | Mean (SD) | p |
| Positiive antibody (%) | | | | | | | | | | | | |
| Anti-TNF dose (mg/kg for infliximab or mg for adalimu | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| mab ) | | | | | | | | | | | | |
| Anti - TNF level (mean, SD) | | | | | | | | | | | | |
| Anti - TNF level /dose (mean, SD) | | | | | | | | | | | | |
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**Last Table:** **Adverse Events Occurring at an Incidence of Greater Than 5% in Either Group**

| | **Inflx + MTX (n=) N (%)** | **Inflx + Placebo (n=)\ N (%)** | **Between group difference % (95% CI)** | **Ada + MTX (n=) N (%)** | **Ada + Placebo (n=)\ N (%)** | **Between group difference % (95% CI)** | **Any anti-TNF + MTX (n=) N (%)** | **Any Anti TNF + Placebo (n=) N (%)** | **Between group difference % (95% CI)** |
|---|---|---|---|---|---|---|---|---|---|
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