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Clinical Response Rates, Placebo Response Rates and Significantly Associated Covariates Are Dependent Upon Choice of Outcome Measure in Hidradenitis Suppurativa: A Post-Hoc Analysis of PIONEER 1 and 2 Individual Patient Data

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Abstract

Background—The Hidradenitis Suppurativa Clinical Response (HiSCR) is the gold standard primary outcome measure for Hidradenitis Suppurativa (HS) clinical trials, however it does not assess the presence of draining tunnels, a common finding in advanced disease. It is unclear what the effect of the presence or absence of draining tunnels has upon the efficacy of adalimumab therapy in moderate and advanced disease.

Objectives—We evaluated the efficacy of adalimumab versus placebo using the International Hidradenitis Suppurativa Severity Score System (IHS4). Additionally, we assessed the impact of draining tunnels upon therapeutic response as measured by both the HiSCR and change in nodule counts.

Methods—Re-analysis was conducted using the IHS4 and PIONEER 1 and 2 Individual Patient Data. Both binary outcomes (achieving HISCR and achieving change in IHS4 severity category) and continuous outcomes (nodule counts and IHS4 score) were calculated using R version 3.5.3. Regression modeling was undertaken to assess the impact of draining tunnels and other variables. $P<0.05$ was considered statistically significant.

Results—The significance of adalimumab therapy was dependent upon the outcome measure used. Placebo response rates were highest when binary outcome measures were used. Draining

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tunnels, smoking, antibiotics and BMI influence HiSCR response in Pioneer 2. Significant differences in disease severity were seen between PIONEER 1 and 2 datasets.

Conclusions—Elevated placebo response rates in PIONEER 1 and 2 are partially attributable to the use of binary outcome measures. Draining tunnels influence clinical response as measured by HiSCR and nodule counts in Pioneer 2. Further investigation into the effect of BMI upon clinical response is required.

Capsule Summary

• The Hidradenitis Suppurativa Clinical Response (HiSCR) clinical endpoint is the gold standard outcome measure in Hidradenitis Suppurativa (HS) clinical trials. The impact of draining tunnels (in advanced disease) upon the measured efficacy of adalimumab in HS is not well described. Other outcome measures (such as the IHS4) include draining tunnels but no direct comparison of outcome measures within a common dataset has been undertaken.

• Clinical response to adalimumab is significantly greater than placebo regardless of the use of outcome measure in PIONEER 2 but not PIONEER 1. Placebo response rates in the PIONEER 1 and 2 Phase 3 trials are significantly lower when the HiSCR is replaced by the IHS4. Draining tunnels, smoking, antibiotic use and BMI are significantly associated with reduced HiSCR response in Pioneer 2 and differences between results of PIONEER 1 and 2 studies are attributable to different disease severities of patient populations.

Keywords

Hidradenitis Suppurativa; Acne Inversa; HiSCR; IHS4; outcome measures; BMI; Tunnels; Placebo

Background

The HiSCR (Hidradenitis Suppurativa Clinical Response)[1] outcome measure is currently considered the gold-standard primary outcome measure for the assessment of new pharmacological interventions in Hidradenitis Suppurativa (HS) clinical trials[1,2]. HiSCR is defined as a 50% reduction in abscess and nodule count without any increase in the number of abscesses or draining tunnels relative to baseline[1]. However, the high rates of placebo response[3] have been identified and are problematic for the evaluation of novel pharmacological interventions in this disease[3]. As such, studies utilizing the HiSCR may be prone to measurement bias when comparing different stages and severities of disease[4]. The International Hidradenitis Suppurativa Severity Score[5] (IHS4: developed by the European Hidradenitis Suppurativa Foundation Investigator Group) is an alternative outcome measure that is often included as a secondary outcome, but the results of this outcome measure have not been reported in any Phase 3 clinical trial to date. There have not been any attempts to compare different outcome measures using the same clinical trial dataset. This comparison would enable the identification of specific clinical variables which may predict response to therapy, and also allow the evaluation of measurement bias within specific outcome measures themselves.

Given the heterogeneous clinical manifestations of HS[6], (including nodules, abscesses, tunnels and scarring), the quantification of abscesses and nodules as an outcome measure

(HiSCR) does not take into account the response of draining tunnels to pharmacological therapy. Given the overall response rates of HS to adalimumab (41.8% and 58.9% in PIONEER 1 and 2 respectively)[7,8] and the significant dropout rates in existing studies due to lack of efficacy (27%50%)[7,8], it is important that we understand the impact of draining tunnels upon treatment efficacy.

We hypothesized that the presence of draining tunnels in HS has no impact upon rates of clinical response to adalimumab therapy. This will be assessed through comparison of two outcome measures (HiSCR and IHS4 – both as binary and continuous variables) within the PIONEER 1 and PIONEER 2 Phase 3 clinical trial dataset at Week 12 compared with Baseline (Week 0). Our specific aims include to evaluate the efficacy of adalimumab versus placebo using the IHS4 outcome measure in place of HiSCR; and to assess the impact of the presence of draining tunnels upon clinical response as measured by the HiSCR and change in nodule counts.

Methods

De-identified individual patient data (IPD) from PIONEER 1 and PIONEER 2 studies[7] were made available by AbbVie Inc and accessed through the secure Vivli online platform. Raw data were extracted and compared to the available published data[7] to ensure accuracy. Only data for 'Time Period A' (Week 0 - Week 12) comparing adalimumab 40mg weekly versus placebo was included in the analysis in order to reflect current dosing recommendations. Individuals with incomplete data, and those who received antibiotic therapy in PIONEER 1 were excluded from analysis. Antibiotic therapy in PIONEER 2 was included as a covariate. Our statistical methods mirrored those of the PIONEER 1 and PIONEER 2 statistical analysis[7] with the exception of the HiSCR (sliding dichotomous variable) being replaced with the IHS4. The IHS4 was expressed as a continuous variable using available raw IPD according to the published equation by Zouboulis et al[5]. (Nodule Count) + (Abscess Count*2) + (Draining Tunnel Count *4). It was also calculated as a sliding dichotomous variable determined by progression to a lower severity category. Severity categories (Mild 0–3; Moderate 4–10; Severe ≥11) were derived from Zouboulis et al[5]. All data analysis was conducted in R version 3.5.3[9].

Each variable of interest was assessed for normality using the Shapiro-Wilk test and histograms. The differences between treatment groups were compared using Welch's t-test for normallydistributed continuous variables and the Mann-Whitney U test for non-normally-distributed continuous variables. Chi-squared and Fisher's exact tests were used for categorical variables. Potential associations with the presence of draining tunnels as well as other *a priori* potential associations (Age, Sex, Hurley stage, smoking status, family history, antibiotic use (for PIONEER 2 only) and BMI) were assessed using logistic regression for HiSCR and binary IHS4, and linear regression for percentage change in IHS4 and absolute change in nodule count. Draining tunnels was not investigated as a covariate in linear or logistic expression where IHS4 was the outcome of interest (due to draining tunnels being a component of the IHS4). $P<0.05$ was considered statistically significant.

RESULTS

Demographic characteristics of the participants included in the statistical analysis are presented in Table 1. The number, percentage and inter-group differences between adalimumab and placebo arms, as measured by the HiSCR, change in IHS4 severity category, change in nodule counts and % change in IHS4 score are presented in Table 2. Statistically significant differences between adalimumab and placebo therapy are seen regardless if HiSCR, change in nodule counts or change in IHS4 score are used as the primary outcome measure (Table 2). Change in IHS4 severity category as an outcome measure only identified statistically significant change in PIONEER 2 (Table 2). Rates of placebo response were markedly lower when continuous variables (as opposed to sliding dichotomous) were used as primary outcome measures (Table 2).

Unadjusted logistic regression identified greater odds of HiSCR with adalimumab compared with placebo in PIONEER 1 (OR=1.98; 95% CI: 1.22, 3.26; p=0.006). When adjusted for covariates, adalimumab therapy displayed greater odds than placebo of association with achieving HiSCR (OR=2.05; 95% CI: 1.25, 3.47; p=0.005). No covariates were statistically significant in altering the odds of achieving HiSCR (Table 3). Adalimumab had increased odds of association with a HiSCR response in unadjusted analysis of PIONEER 2 (OR=3.77; 95% CI: 2.32, 6.19; p<0.0001). Adjusting for covariates, patients receiving adalimumab had a further increase in the odds of achieving HiSCR than placebo (OR=4.22; 95% CI: 2.50, 7.28; p<0.001). Current smokers had reduced odds of achieving HiSCR than non-smokers (OR=0.56; 95% CI: 0.31, 0.98; p=0.04) and the presence of draining tunnels reduced the odds of achieving HiSCR (OR=0.45; 95% CI: 0.25, 0.79; p=0.01). In addition, the use of antibiotics reduced the odds of achieving HiSCR (OR=0.47; 95% CI: 0.23, 0.93; p=0.03) and every unit increase in BMI significantly reduced the odds of achieving HiSCR by 7.1%. (OR=0.93; 95% CI: 0.89, 0.97; p<0.001).

No significant difference in odds ratio was identified between adalimumab and placebo in achieving IHS4 category change in PIONEER 1 (OR=1.58; 95% CI: 0.96, 2.62; p=0.07). Adjusting for covariates, adalimumab still did not significantly increase the odds of achieving IHS4 category change versus placebo (OR=1.69; 95% CI: 1.00, 2.86; p=0.05). Hurley stage 3 disease significantly reduced the odds of achieving IHS4 category change (OR=0.52; 95% CI: 0.30, 0.88; p=0.02). Patients receiving adalimumab had increased odds of achieving IHS4 category change than placebo in PIONEER 2 (OR=2.70; 95% CI: 1.66, 4.43; p=<0.0001). Adjusting for covariates increased the overall odds (OR=2.91; 95% CI: 1.75, 4.91; p<0.0001); with Hurley stage 3 disease (OR=0.57; 95% CI: 0.33, 0.95; p=0.03), increase in BMI (OR=0.95; 95% CI: 0.91, 0.98; p=0.01) and male gender (OR=0.55; 95% CI: 0.31, 0.96; p=0.04) significantly reducing the odds of IHS4 category change.

Linear regression identified adalimumab therapy as associated with a mean alteration in nodule count of 2 at Week 12 compared with placebo (b=−2.38; 95% CI: −4.38, −0.38; p=0.02) in PIONEER 1. Accounting for covariates, the association with Adalimumab remained significant; implying that, all other co-variables being the same, the mean change in nodule count was on average higher by 2 nodules for those with Hurley stage 3 at week 12 compared with Hurley stage 2 (b= 2.23; 95% CI: 0.01, 4.48; p=0.05). PIONEER 2

demonstrated a similar degree of alteration in mean nodule count with adalimumab therapy in unadjusted (b=−2.54; 95% CI: −3.92, −1.16; p=0.0003) and adjusted (b=−2.58; 95% CI: −3.97, −1.19; p<0.001) analysis. The mean change in nodule count was on average higher at Week 12 in the presence of draining tunnels (b=1.87; 95% CI: 0.32, 3.43; p=0.02) compared to the absence of draining tunnels.

Linear Regression identified adalimumab therapy was associated with an average reduction of 18.74% in IHS4 compared to placebo in unadjusted analysis of PIONEER 1 (b=−18.74; 95% CI: −32.97, −4.57; p=0.01). By including covariates, adalimumab treatment was significantly associated with 18.60% reduction in IHS4 compared to placebo (b=−18.60; 95% CI: −33.64, −3.55; p=0.02; Table 4). Unadjusted analysis of PIONEER 2 illustrated a 41.11% reduction in IHS4 with adalimumab compared to placebo (b=−41.11; 95% CI: −56.23, −25.99; p<0.0001). In PIONEER 2, adalimumab therapy was associated with a 39.79% reduction in IHS4 score in adjusted analysis (b=−39.79; 95% CI: −54.92, −24.65; p<0.0001). Each unit increase in BMI (as a continuous variable) attenuated the percentage change IHS4 score by 1.65% (b=1.65; 95% CI: 0.50, 2.81; p=0.01). No other significant covariates were identified.

Discussion

The impact of substituting HiSCR with IHS4 as the primary outcome measure of the PIONEER Phase 3 clinical trials is dependent upon whether the outcome variable is binary or continuous. Substituting HiSCR with change in IHS4 category resulted in no statistically significant difference between adalimumab and Placebo in PIONEER 1 (Table 2). Continuous variables (both nodule counts and IHS4 values) were statistically significant in both studies. Integrating draining tunnel status (using the IHS4) reduced placebo response rates in both PIONEER 1 and PIONEER 2 regardless of if binary or continuous variable was used. The use of the IHS4 as a continuous variable resulted in placebo response rates consistent with studies of Psoriasis and Atopic Dermatitis (4.5%−12%).[12–14] This suggests that the placebo response rate is partially a product of the HiSCR outcome measure (i.e. the use of a binary outcome); as well as the natural variability of inflammatory lesions in HS and inter-rater variation in counting lesions[3]. It is recognized[15] that the use of dichotomous outcomes reduced the power to detect difference between groups, increases the risks of false positives and subsumes the variability in response within a group or cohort[15]. As the IHS4 score is weighted toward abscesses and draining tunnels as opposed to nodules, it can be hypothesized that tunnels are less susceptible to such variability compared to superficial nodules, and hence the resolution of drainage is more indicative of successful therapy.The inter-rater variability of counting nodules has been previously identified as a factor contributing to placebo response rates[3] and recent proposals for outcome measures assessing disease severity which do not include counts[16] may provide a novel approach once validated in larger cohorts. The association of elevated placebo response rates with specific outcome measures is an important finding given the recent non-significant results of clinical trials evaluating C5a antagonists in HS.[3,11] A recent Phase 2b trial concluded IFX-1 was nonsuperior to placebo as measured by the HiSCR with a placebo response rate of 47.2%. Post-hoc analysis identified a significant reduction in draining tunnels compared with placebo as well as quality of life outcomes[11].

Severe disease (assessed by the presence of draining tunnels) was significantly associated with a reduction in achieving HiSCR in PIONEER 2 (Table 3), and Hurley stage 3 disease associated with reduced odds of achieving IHS4 category change (Table 3). In linear regression modeling, Hurley Stage 3 disease was associated with an altered mean change in nodule count in PIONEER 1; and draining tunnels associated with an altered mean change in nodule count in PIONEER 2. These results are consistent with severe disease (manifest either in increased Hurley staging or presence of draining tunnels) being less responsive to adalimumab therapy. BMI was significant in reducing HiSCR achievement, IHS4 category improvement, and percent change in IHS4 in PIONEER 2. Every unit increase in BMI decreased the odds ratio of achieving HiSCR by 7.1% and IHS4 category improvement by 4.9%, and the percentage change in IHS4 by 1.57%. The possibility of weight-based responses to current dosages of adalimumab in HS requires further investigation. Smoking is known to impact the efficacy of adalimumab in Crohn's disease[17] and this is mirrored in HS with our results (Table 3, Pioneer 2 HiSCR).

The presence of any draining tunnels was significantly associated with HiSCR in PIONEER 2 but was not significantly different between adalimumab and placebo groups (Table 1). Therefore, we conclude that draining tunnels is not a confounder upon the effect of adalimumab in HS; but does have a significant association with HiSCR and change in nodule counts. The discrepancies in results between PIONEER 1 and PIONEER 2 studies may be attributable to statistically significant differences in baseline patient characteristics (Supplemental Table 1). Statistically significant differences were seen in race, age, BMI, smoking status, presence of draining tunnel, and the median nodule and draining tunnel counts were significantly lower in PIONEER 2 compared with PIONEER 1. Additionally, Baseline IHS4 scores were higher in PIONEER 1, indicating patients were suffering from more severe disease in PIONEER 1 than PIONEER 2.

The results of our analysis concur with those of Kimball et al[2] in that, draining tunnels are not a confounder upon the effect of adalimumab in HS. However, our results go further in identifying that draining tunnels, smoking status, antibiotic use and BMI do have an effect upon clinical response as measured by HiSCR. These effects are more prominent in PIONEER 2 in the presence of less severe disease suggesting they may influence response to adalimumab in patients with a similar disease severity as those included in PIONEER 2. Employing an outcome measure which integrates draining tunnels (IHS4) identifies individuals with Hurley stage 3 disease as having reduced odds of achieving a change in IHS4 severity category than Hurley stage 2 disease. Stage 3 patients also exhibit a decreased change in nodule counts in the setting of adalimumab therapy, compared to placebo. This suggests that despite the recent discussion regarding the lack of biological correlation between Hurley staging and disease severity[18], that Hurley stage 3 disease has a statistically significant impact upon the reduction of nodules in the setting of adalimumab therapy.

The limitations of this study include the inherent limitations of using clinical trial data, with the PIONEER studies not being an accurate representation of real-life clinical practice. They also exclude the most severe cases of HS given that more than 20 draining tunnels was an exclusion criteria. Additionally, the data analysed only included 12 weeks of therapy, but

independent analysis suggests that reponse at week 12 is associated with clinical response at week 36 of therapy[19].

The potential clinical application(s) of our findings are immediate in that treatment with adalimumab prior to the development of draining tunnels and Hurley stage 3 disease may be more efficacious. The statistically significant association with BMI also suggests that patients with increased BMI may have a decreased clinical response to adalimumab, however it is unclear whether the degree of change (Table 3 and Table 4) reaches clinical significance. Further investigation into the weight-based response to adalimumab in HS is warranted given these preliminary findings.

Conclusions

Adalimumab 40mg weekly is effective in reducing clinical disease activity as measured by both the HiSCR and the IHS4 compared with placebo in participants with Hidradenitis Suppurativa. High placebo response rates may be a product of the use of binary outcome measures such as HiSCR. Regression analyses identified draining tunnels, smoking, antibiotic use and BMI as independent significant associations with clinical response to adalimumab as measured by HiSCR in Pioneer 2. Only BMI was significantly associated with the use of percentage change in IHS4 in Pioneer 2. Future placebo-controlled studies of novel therapies in HS should acknowledge the influence of outcome measure in the interpretation of their data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:
Characteristics of Population in Each of the Trial Data

Table reports N (% in parentheses) with median (25th and 75th percentile) and mean ± SD for age, BMI, nodules, abscesses, draining tunnel counts, and baseline IHS4. P values calculated using chi-squared or Fisher's exact test for categorical variables, Mann-Whitney U test for non-normally distributed continuous data and Welch's t-test for normally distributed continuous data.

Characteristic	PIONEER 1			PIONEER 2		
	Adalimumab	Placebo	P value	Adalimumab	Placebo	P value
N=	144	145		149	140	
Female	85 (59.0%)	100 (69.0%)	0.10	97 (65.1%)	98 (70.0%)	0.45
Male	59 (41.0%)	45 (31.0%)		52 (34.9%)	42 (30.0%)	
White	111 (77.1%)	113 (77.9%)	0.35	130 (87.2%)	110 (78.6%)	0.07
Black	30 (20.8%)	25 (17.2%)		8 (5.4%)	18 (12.9%)	
Other	3 (2.1%)	7 (4.8%)		11 (7.4%)	12 (8.6%)	
Median Age	35.0 (28.0, 45.0)	37.0 (30.0, 47.0)	0.14	35.0 (27.0, 42.0)	35.0 (26.0, 43.3)	0.49
Mean Age	36.5 ± 11.0	38.4 ± 11.4		34.8 ± 10.1	36.4 ± 12.2	
Median BMI	32.1 (27.1, 38.0)	33.9 (28.5, 39.4)	0.07	30.3 (26.3, 36.0)	31.3 (26.8, 36.0)	0.22
Mean BMI	32.9 ± 7.7	34.6 ± 8.1		30.9 ± 6.4	31.8 ± 6.8	
Hurley 2	80 (55.6%)	79 (54.5%)	0.95	76 (51.0%)	79 (56.4%)	0.42
Hurley 3	64 (44.4%)	66 (45.5%)		73 (49.0%)	61 (43.6%)	
Nicotine Use	77 (53.5%)	88 (60.7%)	0.26	96 (64.4%)	99 (70.7%)	0.31
Family History	37 (25.7%)	28 (19.3%)	0.25	36 (24.2%)	39 (27.9%)	0.56
Presence of Draining Tunnels	108 (75.0%)	108 (74.5%)	1.0	99 (66.4%)	87 (62.1%)	0.52
Antibiotics	-	-		27 (18.1%)	28 (20.0%)	0.80
Median Nodules	8 (4.75, 14)	7 (4, 15)	0.88	6 (4,11)	6 (4, 10.25)	0.98
Mean Nodules	11.4 ± 11.1	11.6 ± 14.2		8.2 ± 6.0	8.8 ± 8.0	
Median Abscesses	1.5 (0, 4)	2 (0, 3)	0.77	1 (0, 3)	1 (0, 3)	0.88
Mean Abscesses	2.7 ± 3.3	2.6 ± 3.6		2.0 ± 2.5	2.3 (3.2)	
Median Draining Tunnels	2.5 (0.75, 7)	2 (0, 5)	0.38	2 (0, 4)	1 (0, 4)	0.60
Mean Draining Tunnels	4.5 ± 5.1	3.7 ± 4.3		3.0 ± 4.0	3.5 ± 5.8	
Median Baseline IHS4	26.5 (15, 45.25)	25.0 (12, 40)	0.28	19 (10, 34)	18 (8.75, 32.25)	0.91
Mean Baseline IHS4	34.7 ± 26.8	31.6 ± 27.9		24.2 ± 20.0	27.3 ± 29.3	

Table 2:

Comparing HiSCR and IHS4 (as both binary and continuous variables) as primary outcome measures in PIONEER 1 and PIONEER 2 Phase 3 Randomized Controlled Trial Data

Outcome Measure at Week 12	PIONEER 1			PIONEER 2		
	Adalimumab	Placebo	P value	Adalimumab	Placebo	P value
N =	144	145		149	140	
Number of Patients Achieving HISCR (%)	62 (43.06%)	40 (27.59%)	**P=0.01**	92 (61.74%)	42 (30.00%)	**P<0.0001**
Number of patients Achieving Change in IHS4 Category (%)	53 (36.81%)	39 (26.90%)	P=0.09	76 (51.01%)	39 (27.86%)	**P<0.0001**
Mean Change in AN Counts (Mean % Change from Baseline)	−5.47 (−33.80%)	−2.81 (−13.51%)	**P=0.006**	−5.64 (−50.02%)	−2.24 (−16.01%)	**P<0.0001**
Mean Change in IHS4 Value (Mean % Change from Baseline)	−11.08 (−30.82%)	−4.91 (−12.08%)	**P=0.002**	−10.36 (−46.29%)	−1.33 (−5.18%)	**P<0.0001**

Table 3:

Results of logistic regression models of HiSCR achievement (Model 1) and IHS4 440 category change (Model 2) in patients treated with Adalimumab and Placebo in PIONEER 1 and PIONEER 2.

Variable	**PIONEER 1 Achieving HiSCR**			**PIONEER 2 Achieving HiSCR**		
Model 1	**Odds Ratio**	**95 % CI**	**P value**	**Odds Ratio**	**95 % CI**	**P value**
Adalimumab	**2.08**	**(1.25, 3.47)**	**0.005**	**4.23**	**(2.51, 7.31)**	**<0.001**
Hurley Stage 3	0.91	(0.52, 1.59)	0.74	0.64	(0.37, 1.11)	0.11
Family History	0.77	(0.41, 1.40)	0.40	0.73	(0.39, 1.32)	0.30
Current Smoker	0.98	(0.59, 1.65)	0.94	**0.56**	**(0.32, 1.0)**	**0.05**
Presence of Draining Tunnels	0.63	(0.34, 1.18)	0.15	**0.47**	**(0.26, 0.84**	**0.01**
Antibiotic Use	-	-	-	**0.48**	**(0.24, 0.95)**	**0.04**
BMI	1.01	(0.97, 1.04)	0.74	**0.93**	**(0.89, 0.97)**	**<0.001**
Male Sex	0.85	(0.49, 1.47)	0.57	0.89	(0.49, 1.61)	0.70
Age	1.0	(0.97, 1.02)	0.73	1.0	(0.98, 1.02)	0.97
Variable	**PIONEER 1 Achieving IHS4 Category Change**			**PIONEER 2 Achieving IHS4 Category Change**		
Model 2	**Odds Ratio**	**95 % CI**	**P value**	**Odds Ratio**	**95 % CI**	**P value**
Adalimumab	**1.69**	**(1.00, 2.86)**	**0.05**	**2.91**	**(1.75, 4.92)**	**<0.0001**
Hurley Stage 3	**0.52**	**(0.30, 0.88)**	**0.02**	**0.57**	**(0.33, 0.95)**	**0.03**
Family History	1.02	(0.55, 1.86)	0.96	1.25	(0.70, 2.22)	0.45
Current Smoker	0.82	(0.48, 1.39)	0.45	1.01	(0.58, 1.76)	0.97
Antibiotic Use	-	-	-	0.76	(0.39, 1.47)	0.42
BMI	1.02	(0.99, 1.06)	0.22	**0.95**	**(0.91, 0.98)**	**0.006**
Male Sex	0.73	(0.41, 1.29)	0.29	**0.55**	**(0.31, 0.96)**	**0.04**
Age	1.0	(0.98, 1.02)	0.94	0.99	(0.97, 1.02)	0.63

Table 4:

Linear regression model of change in nodules (Model 1) and % change in IHS4 outcome measure (Model 2) in Adalimumab treated patients in PIONEER 1 and PIONEER 2

Variable	PIONEER 1 Change in Nodules			PIONEER 2 Change in Nodules		
Model 1	**Estimate**	**95 % CI**	**P value**	**Estimate**	**95 % CI**	**P value**
Adalimumab	**−2.36**	**(−4.40, −0.31)**	**0.02**	**−2.58**	**(−3.97, −1.19)**	**<0.001**
Hurley Stage 3	**2.23**	**(−0.01, 4.48)**	**0.05**	−0.17	(−1.63, 1.29)	0.82
Family History	−0.74	(−3.19, 1.72)	0.56	−0.59	(−2.17, 0.99)	0.47
Current Smoker	−1.00	(−3.08, 1.08)	0.35	−0.05	(−1.56, 1.46)	0.94
Presence of Draining Tunnels	1.09	(−1.49, 3.66)	0.41	**1.87**	**(0.32, 3.43)**	**0.02**
Antibiotic Use	-	-	-	1.10	(−0.67, 2.88)	0.22
BMI	−0.04	(−0.18, 0.09)	0.54	−0.01	(−0.11, 0.10)	0.89
Male Sex	−0.46	(−2.67, 1.75)	0.68	0.02	(−1.55, 1.60)	0.98
Age	0.03	(−0.06, 0.12)	0.51	0.03	(−0.03, 0.09)	0.38
Variable	**PIONEER 1 % Change in IHS4**			**PIONEER 2 % Change in IHS4**		
Model 2	**Estimate**	**95 % CI**	**P value**	**Estimate**	**95 % CI**	**P value**
Adalimumab	**−18.60**	**(−33.64, −3.55)**	**0.02**	**−39.79**	**(−54.92, −24.67)**	**<0.0001**
Hurley Stage 3	8.45	(−6.89, 23.80)	0.28	2.54	(−12.83, 17.90)	0.75
Family History	−3.61	(−21.50, 14.28)	0.69	−6.59	(−23.77, 10.59)	0.45
Current Smoker	1.29	(−14.04, 16.63)	0.87	4.68	(−11.71, 21.07)	0.57
Antibiotic Use	-	-	-	16.75	(−2.52, 36.02)	0.09
BMI	0.17	(−0.82, 1.15)	0.74	**1.65**	**(0.50, 2.81)**	**0.01**
Male Sex	10.61	(−5.52, 26.75)	0.20	8.82	(−7.70, 25.34)	0.29
Age	0.27	(−0.40, 0.94)	0.43	−0.04	(−0.72, 0.65)	0.92