SATURN

An exploration of the dynamic interaction between IL-17, IL-17 inhibition with secukinumab and neutrophils in psoriatic arthritis in vitro and ex vivo with exploratory study on the potential role of Vitamin D

CLINICAL TRIAL REPORT

Chief Investigator: Professor Robert John Moots
Sponsor: University of Liverpool
EudraCT Number: 2015-004502-42
ISRCTN Number: 16488621

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1. TITLE SUMMARY

Title:
An exploration of the dynamic interaction between IL-17, IL-17 inhibition with (secukinumab) and neutrophils in psoriatic arthritis in vitro and ex vivo with exploratory study on the potential role of Vitamin D.

EudraCT Number:
2015-004502-42

Sponsor:
The University of Liverpool

Chief Investigator:
Professor Robert John Moots

Final Protocol Version & Date:
Version 6.1, dated 12/07/2019

Description of Agent/Intervention:
Secukinumab 150mg/300mg subcutaneous injection once weekly for the first 4 weeks then 150mg subcutaneous injection 4 weekly for up to 11 months.

Indication Studied:
Patient treatment group consists of patients who have active psoriatic arthritis (fulfilling CASPAR criteria) affecting ≥2 peripheral joints (swollen and tender) that have not responded to at least one standard Disease-modifying ant-rheumatic drugs (DMARDs).
Healthy treatment group consists of healthy control blood samples (matched for gender to the patients and within 5 years mean age within each gender subgroup).

Study design:
This is a 24-month phase II CTIMP, open-labelled, one arm, non-randomised pragmatic clinical and laboratory study designed to investigate, in detail, the clinical and molecular effects of IL-17 and inhibition of IL-17 with secukinumab on neutrophil function in vitro and ex vivo.

Study Period:
24 months in total with 12 months of therapy, and 12 months for staggered enrolment and laboratory investigations. First patient registered 19/01/2017 and the last patient registered was 26/04/2018

Number of Patients to Secukinumab:
The target number was 20, however the final number registered was 19.

Date of report:
06/02/2020

2. ABSTRACT

Purpose:
The aim of this trial was to assess dynamic interaction between IL-17, IL-17 inhibition with secukinumab and neutrophils in psoriatic arthritis in vitro and ex vivo with exploratory study on the potential role of Vitamin D.

Methods and Materials:
SATURN was a phase II trial. Patients who had active psoriatic arthritis affecting ≥2 peripheral joints that have not responded to at least one standard DMARD, and who met the eligibility criteria were recruited to the trial. All patients registered to the patient group were dosed with Secukinumab. Patients were given secukinumab 150mg/300mg subcutaneous injection once weekly for the first 4 weeks then 150mg subcutaneous injection 4 weekly for up to 11 months. The primary outcome was Neutrophil phenotype and lifespan change in function over time. While also analysed was Vitamin D concentration/receptor over time, Clinical Response, Quality of Life and Toxicity.

Results:
20 patients were registered to SATURN, 19 were allocated to secukinumab and 1 to DMARD prior to protocol version 4. The DMARD patient withdrew consent due to a patient decision prior to treatment and therefore in the full analysis set only the 19 secukinumab patients are analysed.

The first primary endpoint is Neutrophil phenotype change over time. There were 7 different receptors analysed, over 4 different visits (Baseline, Week 12, Week 24 and Week 48). CD16 had a statistically significant difference at Week 24 (Estimate=-75810.91, 95% CI=(-112712.83, -38908.99)) and Week 48 (Estimate=-70483.02, 95% CI=(-108854.47, -32111.58)) compared to baseline. CD64 was statistically significant at Week 12 (Estimate=519.54, 95% CI=(142.29, 896.79)) compared to baseline. CD11b had a statistically significant difference as Week 24 (Estimate=32288.53, 95% CI=(1429.21, 63147.85)) compared to baseline. CD18 was statistically significant at Week 48 (Estimate=9920.42, 95% CI=(848.13, 18992.72)) compared to baseline. CD62L had no statistically significant change over time compared to baseline. CD63 was statistically significant at Week 48 compared to baseline (Estimate=13314.37, 95% CI=(2257.74, 24371.01)). Finally CD66b showed a statistically significant change at Week 24 compared to baseline (Estimate=26064.73, 95% CI=(1069.48, 51059.99)).

The second primary endpoint was Neutrophil lifespan over time. The Neutrophil apoptosis was analysed over the 4 time points, in the presence of two cytokines and without. There was no statistically significant change over time.

Secondary endpoints including looking vitamin D receptors and concentrations over time and also in correlation to the Neutrophil phenotype/apoptosis. Vitamin D receptors and concentrations showed no statistically significant differences over time compared to baseline. Spearman's correlations were produced and there were no strong correlations between the Neutrophil phenotypes/lifespan and Vitamin D concentration/receptors.

Quality of life was assessed using the EQ5D overall healthy score (VAS) and overall HAQ score. Over time it can be seen that there is a mean increase in EQ5D and a mean decrease in HAQ, which indicates an improved patient quality of life.

Adverse events and serious adverse events are coded using MedDRA version 19.0. No patients withdrew from treatment due to a toxicity (grade 3+) or SAE. In total the 19 patients on secukinumab reported 18 adverse events. All adverse events reported were below a grade 3. The SATURN trial had no Serious adverse events reported.

Discussion:

In this trial, we have observed high efficacy of the IL-17 inhibitor, secukinumab, not only for skin and joint, but also nails and entheses and patient-reported outcomes (PROMS). In addition, we did not find any significant adverse events, reinforcing the well-established reported safety profile.

In this study, we confirmed that human neutrophils, from either our cohorts of healthy controls or patients with psoriatic arthritis could express IL-17, confirming recent published reports. In addition, we found that IL-17 could neither activate or prime control healthy neutrophils, using the range of assays that we used.

In psoriatic arthritis patients at baseline, there were no significant differences, compared to our age- and sex-matched healthy cohort in the ability of isolated neutrophils to generate ROS (after stimulation with a receptor-dependent and -independent agonist), undergo apoptosis (in the absence or presence of anti-apoptotic cytokines) or phagocytosis of serum-opsonised *Staphylococcus aureus*. There was a slightly decreased ability of neutrophils from psoriatic arthritis patients at baseline to undergo chemotaxis towards IL-8, compared to healthy controls, but this did not reach statistical significance.

Levels of expression of the surface expression of CD11b and CD18 both increased, while surface levels of CD16 decreased in psoriatic arthritis patients during therapy, compared to healthy controls. This would indicate that circulating neutrophil function is activated during treatment, even though disease activity improves.

During therapy, complex regulation of circulating neutrophil function occurs, with metabolic pathways increased (including receptor expression changes) and others decreased (receptor: signalling pathways). It is also a possibility that if local production of IL-8 is decreased via IL-17 inhibition, then fewer neutrophils will leave the circulation: hence there will be greater numbers of activated neutrophils in the circulation.

3. BACKGROUND

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that occurs in approximately 15-20% of patients with psoriasis. As well as joint involvement, extra-articular manifestations, such as severe skin disease may lead to other comorbidities and result in a substantial clinical burden. Early identification with a timely diagnosis and effective treatment is crucial to prevent long-term structural damage and disability. Psoriatic arthritis is one of the spondyloarthritides, which have related but phenotypically distinct clinical feature, and share common immunological and inflammatory components.

Immunologically, dysfunction in the IL-23/17 axis is considered to play a key role in the underlying pathophysiology of PsA *(ref1)*. This has led to the development of targeted therapies that selectively suppress these cytokines, such as secukinumab, a monoclonal antibody that neutralises Il-17. Secukinumab, licensed for use in psoriasis and psoriatic arthritis, has been shown to be a highly effective agent in their management, with many advantages over the standard disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate and leflunomide, that have been the mainstay of therapy in the past. Moreover, the efficacy of secukinumab is comparable, if not greater than, the other biologic TNF inhibitors (TNFi).

Chronic inhibition of specific cytokines has the potential to modulate the immune system in ways that not only are therapeutically beneficial, but expose patients to the potential unwanted adverse effects, such as the risk of reactivation of latent tuberculosis in the case of the monoclonal antibody TNFi. It is therefore important to investigate the interaction of cytokines, their inhibitors and immune system cells not only in vitro, but also in vivo, in patients with disease who are having specific therapy.

In addition to their central role in control of bacterial and fungal infections, it is now recognised that neutrophils also contribute to pro-inflammatory and often tissue-damaging events associated with a range of inflammatory conditions (ref2). Their role in inflammation has been traditionally associated with the release of tissue damaging molecules such as ROS and granule enzymes [ref3], but now also their newly-recognised ability to generate and release a range of pro-inflammatory cytokines and chemokines (ref4). The generation of these latter molecules can result in the further rounds of infiltration and activation of more neutrophils but can also regulate the functions of other cells of the immune system [ref4]. While many of these changes in neutrophil function occur when they infiltrate an inflammatory site and are exposed to local activating agents, changes in the function of these cells can often be detected in circulating cells. For example, in rheumatoid arthritis many intracellular markers of neutrophil activation, such as NF-kB activation are elevated in active disease, but return to normal, healthy control levels during successful treatment (ref6). Furthermore, changes in the transcriptome can be detected in blood neutrophils from patients with rheumatoid arthritis (ref7), systemic lupus erythematosus (ref8) juvenile systemic lupus erythematosus (ref9) and psoriasis (ref10s). Hence, measurement of the functions of blood neutrophils in inflammatory diseases can indicate *in vivo* activation mechanisms and may also report on the change in disease activity (ref11).

In psoriasis, Th17 cells can infiltrate skin lesions and generate IL-17, which then acts upon keratinocytes (ref12), to generate a range of cytokines and chemokines, including IL-8 and CCL20 (ref13). IL-8 (CXCL8) is a powerful neutrophil chemoattractant and results in the infiltration of neutrophils into the skin lesions (ref14) while CCL20 is also a chemoattractant for neutrophils and Th17 cells (ref15). Activated neutrophils themselves can express the chemokines CCL2 and CCL20, which are chemo-attractants for Th17 cells (ref16) and Th17 cells can express CXCL8, thus forming a complex cross-talk activation/amplification network (ref 15). This central role of IL-17 in the pathogenesis of psoriasis forms the basis of treatment strategies based on IL-17 blockade, such as secukinumab, which has shown efficacy in a number of clinical trials (ref17). In this study, therefore, we have measured blood neutrophil functions in psoriatic arthritis patients pre- and post-treatment with secukinumab and compared these functional changes with clinical outcomes. We have also, from a preliminary and exploratory angle, considered how Vitamin D status may impact on this complex interaction.

4. STUDY DESIGN AND DESCIPTION

4.1 Configuration

A phase II exploration of the dynamic interaction between IL-17, IL-17 inhibition with secukinumab and neutrophils in psoriatic arthritis in vitro and ex vivo with exploratory study on the potential role of Vitamin D.

4.2 Interventions

Secukinumab 150-300mg subcutaneous injection once weekly for the first 4 weeks then 150mg 4 weekly for up to 48 weeks.

4.3 Objectives

Primary Aim

The primary aims are to determine the molecular effects of IL-17 and inhibition of IL-17 with secukinumab on:

- Neutrophil phenotype
- Neutrophil Lifespan

Secondary Aims

1. To determine if neutrophil life span and function is associated with vitamin D concentration and vitamin D receipt (VDR) expression in PsA patients.
2. To explore whether vitamin D concentrations and VDR expression influence neutrophil lifespan and function in PsA patients before and after treatment with secukinumab.

Exploratory Aims

1. To identify whether vitamin D status and levels of VDR expression are associated with development of PASI 75 and 90 responses for skin manifestations, ACR20 response for joint manifestations and achievement of PsARC in response to secukinumab in PsA,
2. To evaluate the clinical response of patients with psoriatic arthritis, treated with secukinumab using, NAPSI, PsARC, PASI 75 and 90 and ACR20 response criteria,
3. To evaluate the safety of patients treated with secukinumab in terms of adverse events (AE), serious adverse events (SAE), infections and serious infections, malignancies, acute injection site reactions and potential immunogenicity.
4. To determine if seasonal variation in vitamin D concentration is associated with a) treatment efficacy (ACR20) and b) infection rate in patients receiving IL-17 inhibition.
5. Function and Production of IL-17.

4.4 Eligibility Criteria

Inclusion Criteria

Healthy control group: 10 healthy control blood samples. The healthy controls will be recruited from staff at the University of Liverpool or Aintree University hospitals and who are not taking nor have taken over the preceding 6 months, any immunosuppressive agent including systemic corticosteroids and whose health is otherwise good. There will be an equal balance of males to females. Matching to biologic or DMARD controls is not required. The healthy controls will provide one sample of blood for neutrophil studies.

Patient secukinumab treatment group: 20 patients with active psoriatic arthritis (fulfilling CASPAR criteria) affecting ≥2 peripheral joints (swollen and tender) that have not responded to at least one standard DMARDs.

1. All meet CASPAR criteria for diagnosis of PsA
2. Be rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) negative at screening
3. Have had no prior exposure to biologic therapy
4. Not have received parenteral glucocorticosteroids in the 6 weeks prior to the baseline assessment
5. If taking oral glucocorticoids remain on a stable dose of <10mg throughout the study with no change to dose in the 6 weeks prior to baseline assessment
6. If taking methotrexate or other DMARDs remain on a stable dose throughout the study and not have change dose or therapy for 6 weeks prior to baseline assessment.

All participants will be adult individuals who are able to give informed consent and aged over 18 years.

Exclusion Criteria

Patient secukinumab treatment/control group:

1. Active or chronic infection including mycobacterium tuberculosis, HIV, hepatitis B or C.
2. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis according to local practice/guidelines) or a positive QuantiFERON TB-Gold test or TB-Spot Test (as indicated in Section 4.1 and Table 6-1). Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
3. Absence of active psoriatic arthritis.
4. Patients who are starting anti-TNF therapy for treating PsA.
5. Patients who have previously been treated with TNF α inhibitors (investigational or approved).
6. Pregnancy and planning pregnancy

- WOCBP who are unwilling or unable to use acceptable methods to avoid pregnancy for study duration plus timeframe as specified in study protocol section 5.2.5.
- Women who are pregnant or breastfeeding.
- Sexually active fertile men not using effective birth control if their partners are WOCBP.

7. Malignancy: History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratosis that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
8. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician.
9. Patients with hyponatraemia and nephrotic syndrome.
10. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor.
11. Use of any investigational drug and/or devices within 4 weeks before registration or a period of 5 half-lives of the investigational drug, whichever is longer.
12. Significant comorbidity that, in the opinion of the investigator, would impact on ability to participate.
13. Any change in the dose of oral glucocorticosteroids or DMARDS in the prior 6 weeks prior to the Baseline visit or use of i.v. intramuscular or intra-articular glucocorticosteroids during the last 6 weeks prior to the enrolment visit.
14. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes.
15. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, and anti-CD19).
16. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy.
17. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromised the patient and/or place the patient at unacceptable risk for participation in an immunomodulatory therapy.
18. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV), and uncontrolled diabetes.
19. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrolment/registration, to rule out laboratory error

- If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed 1.6 mg/dL (27 µmol/L).

20. History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L).
21. Screening total white blood cell (WBC) count < 3 000/µL, or platelets < 100 000/µL or neutrophils < 1 500/µL or haemoglobin < 8.5 g/dL (85 g/L).
22. Active systemic infections during the last 2 weeks (exception: common cold) prior to registration.
23. Known infection with human immunodeficiency virus, hepatitis B or hepatitis C at Screening or registration.
24. Use of Vitamin D containing supplements.
25. Inability or unwillingness to undergo repeated venepuncture (e.g. because of poor tolerability or lack of access to veins).
26. Patients who have received a live vaccine within 4 weeks prior to planned registration.

4.5 Sample Size Estimate

There are no existing data to allow a formal power calculation. The investigators and sponsor have therefore taken formal advice from Dr Trevor Cox (Previous Director of Statistics, Liverpool Clinical Trials Unit) and used their experience in neutrophil biology and recently published experience in a similar study investigating another cytokine in rheumatoid arthritis (Wright HL, Cross AL, Edwards SW, Moots RJ. Effects of IL-6 and IL-6 blockade on neutrophil function in vitro and in vivo. Rheumatology (Oxford). 2014 Jul; 53(7):1321-31). From this, it is believed that studying 20 patients taking secukinumab and 10 healthy controls will allow detection of a biologically relevant signal in this new study. These numbers will also provide important pilot data on potential relationships of clinical effects of vitamin D, in addition to laboratory effects, informing a further definitive trial.

4.6 Randomisation Procedure

Generation of sequence

Per protocol v3 and earlier, patients are allocated to treatment versus no treatment (patients randomised to no treatment will still receive standard care) in a 4:1 ratio by means of computer generated random permuted blocks of size 5, created by the Liverpool Cancer Trials Unit (LCTU) in accordance with their standard operating procedure employing the Stata add-in ralloc. Due to the small number of patients included and the unbalanced nature of the study, a fixed block length of size 5 is used and no stratification factors are included.

From protocol v4, onwards the standard care arm was dropped, and a planned 20 patients are recruited to secukinumab. Brief descriptive statistics will be provided for any patients recruited prior to protocol v4 being approved who were randomised to the standard care arm.

Concealment & implementation of sequence

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria shall be registered at site using a pre-generated list produced by the trial statistician at the Liverpool Clinical Trials Unit. The trial is open-labelled.

A component of the study dictates that 10 healthy controls are recruited to compare against the cohort of 20 patients receiving secukinumab. Here five male and five female patients will be matched by age to the respective cohort of male and female patients to receive secukinumab. Healthy volunteers shall be selected from amongst the staff at the University of Liverpool or Aintree University and shall be matched so that the volunteer age is within 5 years of the median age of the respective group of patients receiving secukinumab.

4.7 Blinding

Not applicable as this is a single-arm study with no blinding.

4.8 Endpoints

Primary:

Neutrophil phenotype and lifespan function changes over time.

Neutrophil phenotype
Measured in the following receptors:

- CD16
- CD64
- CD-11b
- CD18
- CD62L
- CD63
- CD66b

Neutrophil Lifespan
Measured as cell apoptosis (percentage of dead cells)

Secondary:

1. To determine if neutrophil lifespan and function is associated with Vitamin D concentration and VDR expression in PsA patients, and
2. To explore whether Vitamin D concentrations and VDR expression influence neutrophil lifespan and function in PsA patients before and after treatment with Secukinumab.

Vitamin D Status

Vitamin D status clinical measure.

Surface Vitamin D Receptor
Surface Vitamin D receptor (VDR).

Exploratory:

1. A clinical response in patients with psoriatic arthritis using NAPSI, PsARC, PASI 75, PASI 90 and ACR20 criteria.
2. Reports of AEs, SAEs, infections and serious infections, malignancies, acute injection site reactions and potential immunogenicity.

Disease Indices
ACR20, PASI 75, PASI 90 and NAPSI are scores based on clinical response of psoriatic arthritis to treatment.

Patient Reported Outcomes
EQ5D and HAQ questionnaires are completed by patients.

Safety:
AEs and SAEs reported at study visits.

4.9 Trial Oversight Committees

Trial Steering Committee
The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. In particular, the TSC will concentrate on the progress of the trial, adherence to the protocol, patient safety and consideration of the new information. The TSC must be in the agreement with the final protocol and, throughout the trial, will take responsibility for:

a) Major decisions such as need to change the protocol for any reason
b) Monitoring and supervising the progress of the trial
c) Reviewing relevant information from other sources
d) Considering recommendations from the ISDMC (if required)
e) Information and advising the TMG on all aspects of the trial.

The TSC will include experienced arthritis clinicians, other medical experts and those experienced in clinical trials.

The TSC is limited and includes an independent Chairman and two additional independent expert members (one being a statistician) and a lay/consumer representative, along with members of the Trial Management Group (TMG).
Independent Safety Data Monitoring Committee

The need for an ISDMC has been considered as part of the risk assessment and has been determined as unnecessary as this is a short trial, conducted at a single site, using a known drug considered safe with license.

The TMG and the TSC will take on the responsibility for assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. However, if there is a high number of Serious Adverse Events reported (>than 6 SAE's in 12-month period), an 'Ad Hoc' ISDMC will need to be convened to specifically look at safety.

In this situation, the 'Ad Hoc' IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

Adjudication Committee

Not applicable, there is no adjudication committee for this study.

4.10 Planned Interim Analysis

Given the small number of patients are going to be recruited, and an expected recruitment duration of 12 months; no formal interim analyses are planned.

5. TRIAL HISTORY

5.1 Quality Control and Data Validation Procedures

Central and site monitoring is conducted to ensure protection of patients participating in the trial, trial procedures, trial intervention administration, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

Registration checks
Generation of the registration list will be reviewed (ST002_CHK1.1) to ensure provision of adequate registration numbers.

5.2 Protocol Amendments

Below are the 8 amendments that occurred throughout the course of the study.

Substantial Amendment 1 (prior to greenlight) – protocol v3.0, 25th February 2016: protocol and PIS amended following MHRA review. Summary of changes:

- Additional detail on the requirement for participants of child bearing potential or male participants with partners of child bearing potential to use effective contraception for the duration of the trial and outlining the length of time following completion of the medication that participant would need wait prior to planning pregnancy.
- Addition of monthly pregnancy tests extra to the initial one performed at screening
- Modification of the tuberculosis assessment and addition of the tests to screening
- Clarification of the complete physical examination performed at screening and subsequent trial visits to add major organ systems and lymphadenopathy
- Addition of the vital signs checks (Heart Rate, Blood Pressure, Body Temperature) at screening and subsequent trial visits to comply with leflunomide SmPC
- Live vaccines was added to the list of exclusion criteria
- Addition of a final follow-up one month after the last treatment dose.

The PIS was also amended (Patient PIS version 3.0 dated 16th March 2016) to incorporate the requirement for pregnancy tests and for effective contraception for sexually active participants.

Substantial Amendment 2: the following documents were updated:

- Protocol v4.0 (9th December 2016) (see amendment details below)
- Patient-PIS v4.0 (5th December 2016) to reflect the change in registration process
- Health control-PSI v3.0 dated 9th December 2016 to reflect change in registration process
- GP letter v3.0 (9th December 2016) to reflect the change in registration process

Protocol amendment summary:

- Simplification of the inclusion/exclusion criteria
- Inclusion of patients who failed at least on DMARD treatment instead of two
- Removal of the exclusion of patients taking high-potency opioid analgesic (e.g. methadone, hydromorphone, morphine)
- Patient-PIS v4.0 (5th December 2016) to reflect the change in registration process
- Healthy control-PSI v3.0 dated 9th December 2016 to reflect the change in registration process
- GP letter v3.0 (9th December 2016) to reflect the change in registration process
- Replacement of the randomisation process by a simple registration for Secukinumab, to be compared to non-study patients receiving DMARD alone. For the stud primary outcome randomisation was not required. Patients who prefer to stay on oral medication rather than a parenteral drug, or who do not like the thought of having a novel biologic, will be recruited outside of the SATURN trial as part of another research study for which the chief investigator has ethical approval to perform neutrophil measurements.

Substantial Amendment 3

- SmPC – Update to section 4.8 Secukinumab change 1 - 05/04/2017
- SmPC – Update to section 4.8 Secukinumab change 2 –25/07/2017
- SmPC – Update to section 4.8 Secukinumab change 3 - 01/09/2017
- Reference Safety Information version 3

Substantial Amendment 4

- Protocol summary: main inclusion criteria: change “at least two standard DMARD, and” to “at least one standard DMARD.
- Protocol summary: Study design and Analysis plan, phase 1 and phase 2: assessment time should be in weeks instead of months
- Protocol: through-out the protocol assessment time should be in weeks instead of months
- SAE section: remove the possibility for site to use the online LCTU PV system. Sites are to use paper SAE and AE form, TC will enter information on LCTU PV system.
- Oversight Committees: change to reflect the fact that SATURN has a joint TSC/ISDMC in section 16 and 17.
- Updated Blood Samples Patient Group (8.5.1) as it was not consistent with the Schedule of trial Procedures (8.1).

- Updated new Personnel – Trial Statistician and Trial Coordinator
- ISRCTN number on first page updated
- Exclusion criteria: correct numbering
- Patient Information Sheet
- Informed Consent Form
- Patient Information Sheet Re Consent
- Patient treatment diary (version 1 dated 10/05/2016)

Non-Substantial Amendment 5

- Update to SmPC Secukinumab 09/10/2018

Non-Substantial Amendment 6

- Update to SmPC Secukinumab 12/11/2018

Non-Substantial Amendment 7

- Revised Study end date 01 Jul 2019

Substantial Amendment 8

- The purpose of amendment 8 was to clarify the 'End Points of the Trial'.

5.3 Trial Milestones

- First patient was registered on: 19/01/2017
- Last patient was registered on: 26/04/2018
- Date of data lock: 25/10/2019
- Total number screened to data lock date: 48
- Total number registered to data lock date: 20
    - Secukinumab: 19
    - DMARD: 1
- Total number withdrawn from study to data lock date: 1

6. PATIENT FLOW AND TRIAL CLOSURE

The SATURN trial was open to recruitment, between October 2016 and April 2018, a total of 48 patients were screened for eligibility, of which 19 received secukinumab and 1 was allocated the DMARD only arm (prior to protocol version 4).

7. PROPOSED METHODOLOGY

Statistical analyses will be performed using Stata v14 or higher or other appropriate statistical software. Though not included in v4 of the study protocol, it is planned that the final analysis will be performed when all patients have completed study treatment and results for primary endpoint data are available.

7.1 Patient Groups for Analysis

Full Analysis set:

In order to follow the Intention to Treat (ITT) principle this will consist of all registered patients except for:

a) Patients withdrawing consent between registration and starting therapy
b) Patients withdrawn from the study after registration because of irregularities with the consent process
c) Patients whose information determining ineligibility existed before registration but was not read until after registration.

Per protocol (PP) set:

This will consist of those patients in the Full Analysis set without any major deviations in treatment or assessment that could affect the outcome. This population will be used in a sensitivity analysis for the primary endpoint should >20% (i.e. >4 patients) experience a major deviation from protocol treatment.

Safety set:

All patients who received any trial treatment according to the treatment received will be used for analysis of toxicity and adverse events.

7.2 Handling Dropouts

If a registered patient drops out of the study before treatment starts, they will be replaced. The chance of this occurring is thought to be small.

7.3 Identification and Handling of Outliers

For continuous variables potential outliers will be defined as:

Mild outliers:	UQ+1.5×IQR	to	UQ+3×IQR
	LQ-1.5×IQR	to	LQ-3×IQR

Severe outliers: values more extreme than the above

(Note: UQ=Upper Quartile, LQ=Lower Quartile, IQR=Inter Quartile Range)

If transformation to normality removes the apparent outliers then no action will be taken apart from use of the transformation if normality is required for a particular statistical procedure, or to remove the leverage effect of the outlying values.

The appropriate transformations will be chosen using “ladder of powers” approach using the Stata command ladder. Otherwise potential outliers will be queried but no action taken if the result is not amended. No procedure will be adopted for outliers in categorical or ordinal data.

Continuous data will be displayed using box and whisker plots with outliers identified.

7.4 Study Centre Effects

Not applicable as there is only one participating study centre.

7.5 Adjustment for Covariates

As this is an exploratory study with a small number of patients, there will be no formal adjustment for covariates.

7.6 Multiplicity Adjustments

As this is an exploratory study, there will be no formal adjustment for multiple comparisons.

7.7 Missing Data

The amount of missing data is expected to be small so no methods for imputing missing data will be applied due to the small size of the study.

7.8 Sensitivity Analyses

No planned sensitivity analyses will be performed as it is expected that the majority of patients will follow the study protocol without major deviations. However, if >20% of the study population (i.e. >4 patients) experience a major deviation from the protocol, then a per protocol analysis will serve as a sensitivity analysis for the primary endpoint only.

7.9 Pre-Specified Subgroup Analyses

There are no pre-specified subgroup analyses.

7.10 Definition & Derived Variables

As this is a small exploratory study of lab, clinical data, quality of life and toxicity, there are no derived variables and all data shall be analysed in their raw form.

7.11 Specification and Estimation of Efficacy Parameters

Table 1: Summary of Outcome variables and corresponding efficacy parameters			
Outcome variable	**Efficacy parameter**	**Comment**	**Method**
Primary Endpoints:			
Neutrophil phenotype	Model estimates and 95% confidence intervals, measured at each time point using the outcome Mean Fluorescence Intensity (MFI) for each receptor. Accompanied by another model estimates and 95% confidence intervals, addressing the change in MFI from baseline over time, for each receptor.	7 receptors measured: CD16 CD64 CD-11b CD18 CD62L CD63 CD66b	Longitudinal analysis
Lifespan	Model estimates and 95% CI, measured at each time point using the outcome apoptosis measured with and without added cytokine. Accompanied by another model estimates and 95% CI, addressing the change in apoptosis from baseline over time, with and without the added cytokine.	Apoptosis will be measured with and without added cytokines to see if apoptosis (lifespan) is altered.	Longitudinal analysis
Secondary Outcomes			

Vitamin D concentration	Model estimates and 95%CI, measured at each time point using the outcome Vitamin D concentration. The link between Vitamin D and the neutrophil phenotypes and lifespan over time will be assessed via correlation plots	Vitamin D had an additional measurement at week 36.	Longitudinal analysis. Panel correlation plots.
Vitamin D Receptor (VDR)	Model estimates and 95% CI measured at each time point using the outcome Vitamin D receptor (in neutrophils and other). The link between VDR and the neutrophil phenotypes and lifespan over time will be assessed via correlation plots	VDR expression was assessed on neutrophils and other. The other consists of a mixture of either lymphocytes or monocytes.	Longitudinal analysis. Panel correlation plots.
Exploratory Endpoints			
Clinical response of psoriatic arthritis to treatment	ACR20 / PsARC / PASI 75 / PASI 90 / NAPSI All collected at baseline, 12, 24, 36 and 48 weeks. Provide model estimates and 95% CI over time.		Longitudinal analysis techniques
Quality of Life	Components counts, percentages and mean (95% CI) will be presented for both the EQ5D and HAQ. The overall HAQ and overall health score (VAS) will be summarised by mean (95% CI)	QoL is split into two separate questionnaires the EQ5D and the HAQ Both collected at baseline, 12, 24, 36 and 48 weeks	Summary statistics

Toxicity	None.	Adverse events (AE), serious adverse events (SAE), infections and serious infections, malignancies, acute injection site reactions and potential immunogenicity.	Summarised as the number of patients n, (%) to have each event

8. STUDY RESULTS

8.1 Recruitment and Disposition

Table 2 provides a recruitment summary.

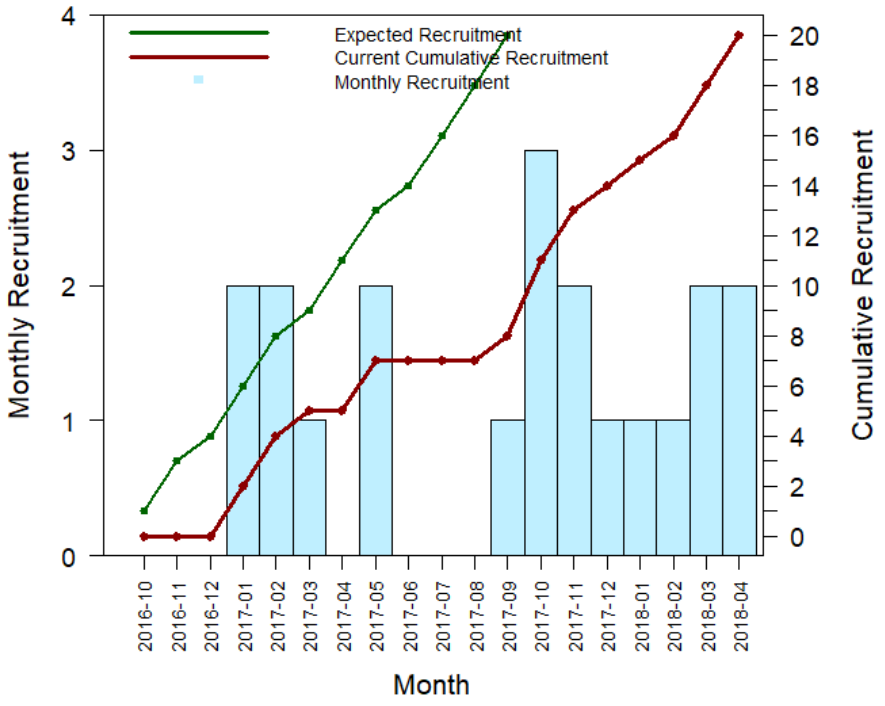
Table 2: Recruitment Summary	
Date of greenlight*:	14/10/2016
Number of patients eligible:	48
Number of patients declined:	18
Patients registered to Secukinumab:	19
Patients registered to DMARD only:	1
*The trial coordinator and/or chief investigator have completed the initiation visit at site. Research staff including research nurses have been fully initiated and have signed the delegation log and initiation log. All staff have been fully trained by the chief investigator and/or trial coordinator; All regulatory and ethical approvals are in place; All signatures are complete and all documentation is in place; The research site agreement is signed by all parties; The CRFs are at site; The drug has been released to site.	

(Created using TrialIDLookup, R_SATURN_Registration1 and Sect2_Recruitment found on Statistics Server by RG on 29OCT19:09:16:55.)

10 of the patients screened as eligible are healthy volunteers.

Figure 1 shows expected against study recruitment, both cumulatively and by individual month.

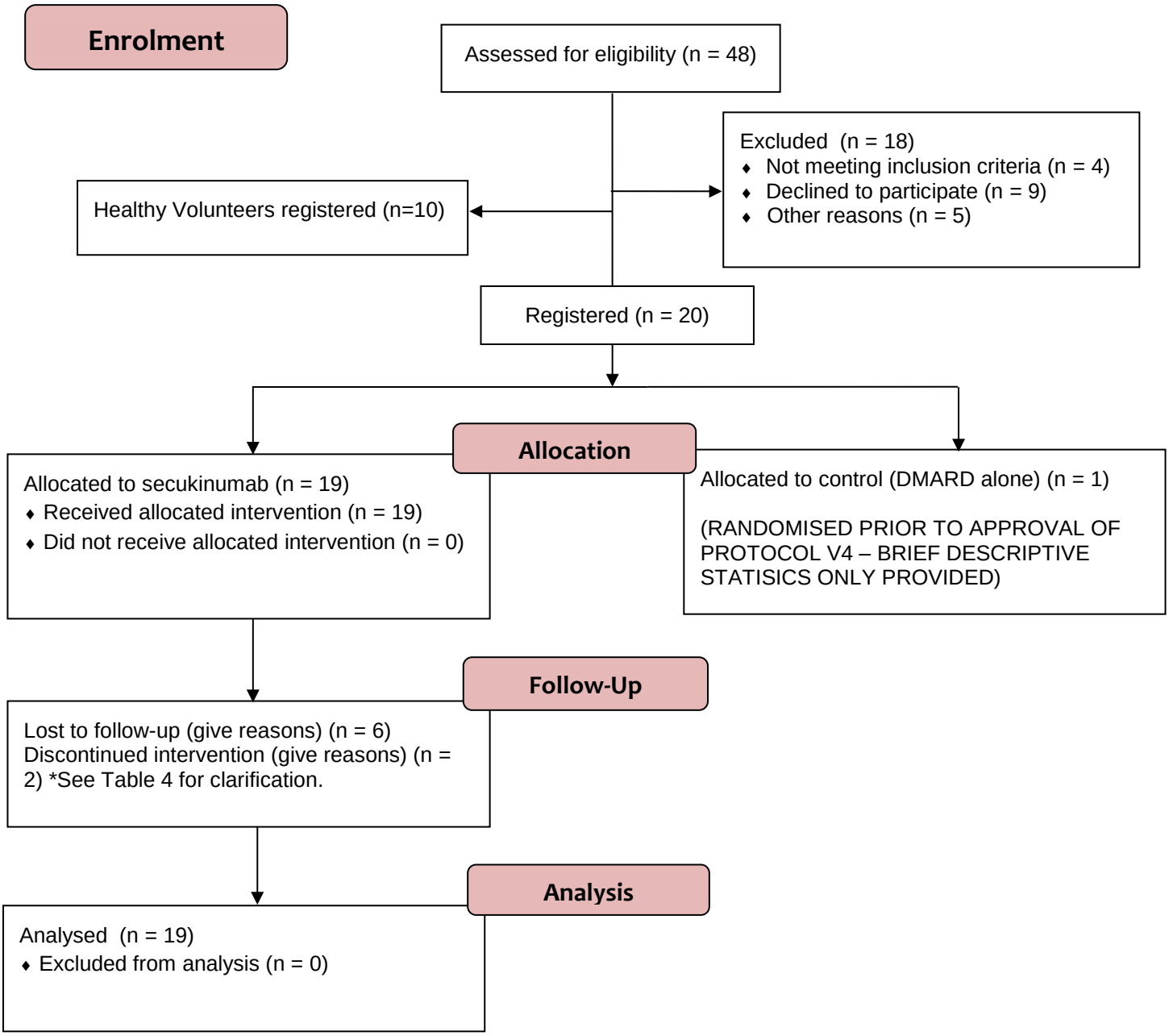
Figure 1: Recruitment Graph



(created using R_SATURN_Registration1 found on Statistics Server by RG on 29OCT19:09:36:57.)

Figure 2, displays a diagram of patients assessed for eligibility, and the numbers registered, receiving treatment, and included in analysis.

Figure 2: Patient Disposition



Loss to follow-up reasons:

- 1 patient failed to attend their week 12 visit and were unable to contact.
- 1 patient failed to attend their week 24 visit and were unable to contact.
- 4 patients completed week 48 treatment but did not attend their week 52 follow-up (3 unable to contact and 1 had AE flare up and so was seen in clinic routinely therefore missing week 52).

Discontinued intervention: Both were due to being lost to follow-up.

8.2 Assessment of Data Quality

A summary of missing CRFs is provided in Table 3.

Table 3: Missing CRFS	
Total number of CRF forms expected:	2290
Number of CRF forms received to date:	2290
Percentage of missing CRF forms:	0
Number of outstanding data queries:	0

A line listing of patients withdrawing from treatment and being lost to follow-up is provided in Table 4.

Table 4: Line listing of withdrawals and losses to follow-up	
End of treatment / loss to follow-up reason	**Secukinumab N = 19**
Other – lost to follow up	2
Total withdrawn from trial	
Withdrew consent no follow-up	0
Lost to follow-up	6

A summary of the number of major and minor protocol deviations is provided in Table 5.

Table 5: Summary of Deviations			
Type	**Description of Deviation**	**Category**	**Secukinumab N = 19**
Major*	Entered but did not satisfy the entry criteria	1	0
	Developed withdrawal criteria but not withdrawn	2	0
	Received an excluded concomitant treatment	3	0
	Received the wrong treatment or incorrect dose	4	0
	Deviation from patient management/assessment	5	1
	Other	6	0
Minor	Protocol Deviations not expected to have an impact on defined endpoints of the trial	7	4
Missing			
*These need to have a potentially major impact on the primary endpoint, such as: a) extent of treatment deemed inadequate b) missing primary endpoint, stratification variables or preplanned covariates			

The major deviation listed above relates to a week 16 pregnancy test that was not completed. Due to the treatment being temporarily halted, the site thought that the pregnancy test was not applicable here. Site was made aware they were not adhering to protocol and the deviation was raised.

The number of patients for whom there was a major protocol deviation is provided in Table 6.

Table 6: Number of Patients with Major Deviations	
No. of Major Deviations	**Secukinumab N = 19**
0	18
1	1

Details of data missing on primary and secondary outcomes are provided in Table 7.

Table 7: Available Data Description						
Patients missing values on:	**Secukinumab N=xx**					**Overall N=xx**
	Baseline	**Week 12**	**Week 24**	**Week 36**	**Week 48**	
Primary Outcomes						
Neutrophil phenotype – receptors						
CD16	0	0	0	NA	1	1
CD64	1	0	0	NA	1	2
CD-11b	0	0	0	NA	1	1
CD18	0	0	0	NA	1	1
CD62L	0	0	0	NA	1	1
CD63	0	0	0	NA	1	1
CD66b	0	0	0	NA	1	1
Neutrophil lifespan						
Neutrophil lifespan (20hr)	0	0	0	NA	1	1
Neutrophil lifespan (20hr added cytokine gmcsf)	0	0	0	NA	1	1
Neutrophil lifespan (20hr added cytokine tnf)	0	0	0	NA	1	1
Secondary Outcomes						
Vitamin D status	0	0	0	0	0	0
Vitamin D receptor (Neutrophils)	0	0	0	NA	1	1
Vitamin D receptor (Other)	0	0	0	NA	1	1

Exploratory Outcomes						
Disease Indices						
PsARC	0	0	0	0	0	0
ACR20	0	1	0	0	0	1
PASI 75	0	0	0	0	0	0
PASI 90	0	0	0	0	0	0
NAPSI	0	0	0	0	0	0
Patient Reported Outcomes						
EQ5D	0	0	0	0	0	0
HAQ	0	0	0	0	0	0

(Created using R_SATURN_Registration1, DO_NOT_DELETE_Transfer_Log, STUFYVISIT, R_SATURN_EndStudy, R_SATURN_SurfaceRec, R_SATURN_Apoptosis, R_SATURN_VitaminDForm, R_SATURN_ClinicalAss1, R_SATURN_ClinicalAss2, R_SATURN_ClinicalAss3, R_SATURN_ClinicalAss4, R_SATURN_Bloods1, R_SATURN_EQ5D and R_SATURN_QOL_HAQDI found on Statistics Server by RG on 29OCT19:10:53:15.)

Details of registration checks are provided in Table 8 with a line listing of registration errors discovered in Table 9.

Table 8: Registration Checks	
	Result
Are registration numbers in MACRO database in correct date order?	No
Are there missing registration trial numbers	No

Table 9: Registration Errors discovered	
Errors discovered	**Action taken**
Patient (person ID 2) was registered after patient (person ID 1), but has an earlier registration trial number	As the registration trial number is the same as the screening number it is common for it to not be in date order. Therefore, no action was taken.

8.3 Description of Baseline Subject Characteristics

Baseline demographic data are provided in Table 10.

Table 10: Baseline characteristics				
Demographic Characteristics		**Secukinumab N = 19**	**DMARD only N= 1**	**Overall N = 20**
Age (years), median (IQR):		50.0 (37.0 to 65.0)	49.0 (49.0 to 49.0)	49.5 (37.5 to 61.5)
Sex, n (%):	Female	10 (52.6)	0 (0.0)	10 (50.0)
	Male	9 (47.4)	1 (100.0)	10 (50.0)
Ethnicity, n (%):	White	19 (100.0)	1 (100.0)	20 (100.0)
Smoking status, n (%):	Current smoker	5 (26.3)	0 (0.0)	5 (25.0)
	Ex-smoker	5 (26.3)	0 (0.0)	5 (25.0)
	Non-smoker	9 (47.4)	1 (100.0)	10 (50.0)
Alcohol Status, n (%):	None	5 (26.3)	0 (0.0)	5 (25.0)
	Sporadic	10 (52.6)	1 (100.0)	11 (55.0)
	Regular	4 (21.1)	0 (0.0)	4 (20.0)
	Excessive	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg), median (IQR):		86.1 (66.9 to 106.0)	79.5 (79.5 to 79.5)	82.9 (67.3 to 104)
Height (cm), median (IQR):		168.0 (163.0 to 174.0)	175.0 (175.0 to 175.0)	169.0 (163.0 to 174.5)

(Created using R_SATURN_Registration1 and R_SATURN_DEMOGRAPHICS found on Statistics Server by RG on 29OCT19:11:21:48.)

8.4 Exposure to Treatment & Compliance

Per protocol, total dose is Secukinumab 150-300mg subcutaneous injection once weekly for the first 4 weeks then 150mg 4 weekly for up to 48 weeks. No dose modification should be used for the secukinumab arm.

Details of treatment exposure and compliance are provided in Table 11.

Table 11: Treatment Exposure	
Measure	**Secukinumab (N=19)**
Number of Dose/Patient	13.95
Mean Dose/Patient	2186.84 mg

Table 11: Treatment Exposure	
Measure	**Secukinumab (N=19)**
Number Pts completing week:	
1	19
2	19
3	19
4	19
8	18
12	16
16	17
20	18
24	18
28	17
32	17
36	17
40	17
44	17
48	17

(Created using R_SATURN_Registration1, R_SATURN_treatinduction, R_SATURN_treatmaint and studyvisit found on Statistics Server by RG on 29OCT19:11:34:09.)

8.5 Analysis of Primary Outcomes

Tables 12-18 and Figures 3-9 give summary results for each neutrophil phenotype receptor at each study visit.

CD16

Table 12a: Results for Primary Outcome – CD16				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	254688.24 (22584.30)	(207240.38, 302136.10)	-
	Visit (Baseline)	-	-	254688.24 (209303.38, 300073.09)
	Visit (Week 12)	-31383.32 (18363.04)	(-68285.24, 5518.60)	223304.91 (177254.44, 269355.38)
	Visit (Week 24)	-75810.91 (18363.04)	(-112712.83, -38908.99)	178877.33 (132826.86, 224927.80)
	Visit (Week 48)	-70483.02 (19094.31)	(-108854.47, -32111.58)	184205.21 (136968.98, 231441.45)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:08:52:34.)

Table 12a summarises both the model estimates and the least squares estimate. The LSE shows that over time Mean Fluorescent Intensity of CD16 decreases. However, interpretation of statistical significance comes from the model estimates. From this model, it indicates that in relation to CD16, there is a statistically significant difference at Week 24 and Week 48 compared to baseline, at the 5% level.

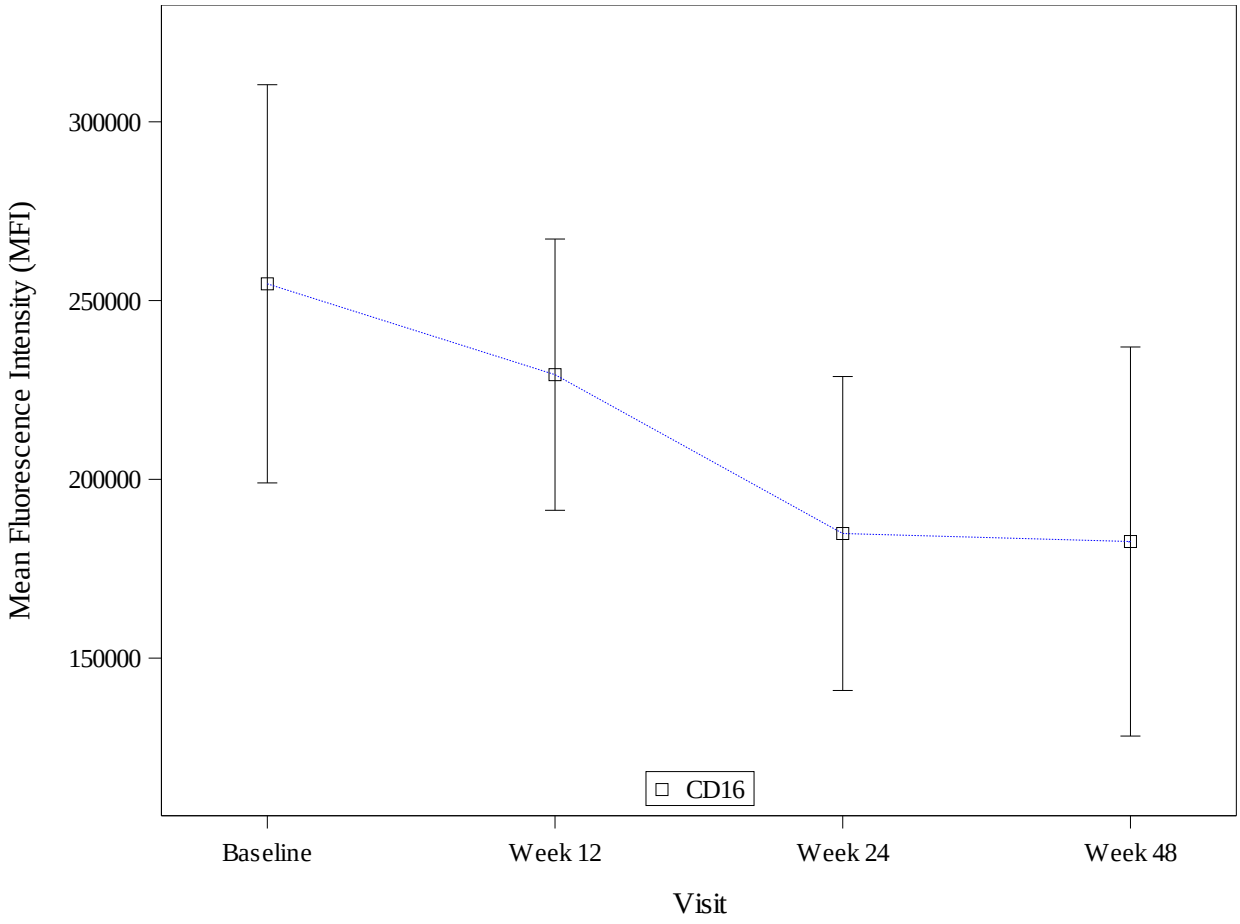
Table 12b: Results for Primary Outcome – CD16 (Change from Baseline)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	91039.04 (35111.89)	(16605.16, 165472.92)	-
	Baseline CD16	-0.48 (0.12)	(-0.73, -0.22)	-
	Visit (Week 12)	-	-	-31693.66 (-64158.36, 771.04)
	Visit (Week 24)	-44427.58 (16443.24)	(-77921.38, -10933.79)	-76121.24 (-108585.94, -43656.54)
	Visit (Week 48)	-40465.29 (17122.52)	(-75342.72, -5587.85)	-72158.95 (-105995.15, -38322.74)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:08:54:48.)

From Table 12b, you can see a statistically significant difference in the change from baseline to Week 24 and Week 48 compared to change from baseline to Week 12. This is also indicated in Figure 3, by the large drop in CD16 MFI.

Figure 3: Graph of raw mean CD16 against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.
*Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:14:36:26.

CD64

Table 13a: Results for Primary Outcome – CD64				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	4296.74 (309.71)	(3646.06, 4947.42)	-
	Visit (Baseline)	-	-	4296.74 (3674.02, 4919.46)
	Visit (Week 12)	519.54 (187.63)	(142.29, 896.79)	4816.28 (4192.06, 5440.50)
	Visit (Week 24)	237.24 (187.63)	(-140.02, 614.49)	4533.97 (3909.76, 5158.19)
	Visit (Week 48)	607.47 (195.20)	(215.01, 999.94)	4904.21 (4270.99, 5537.43)

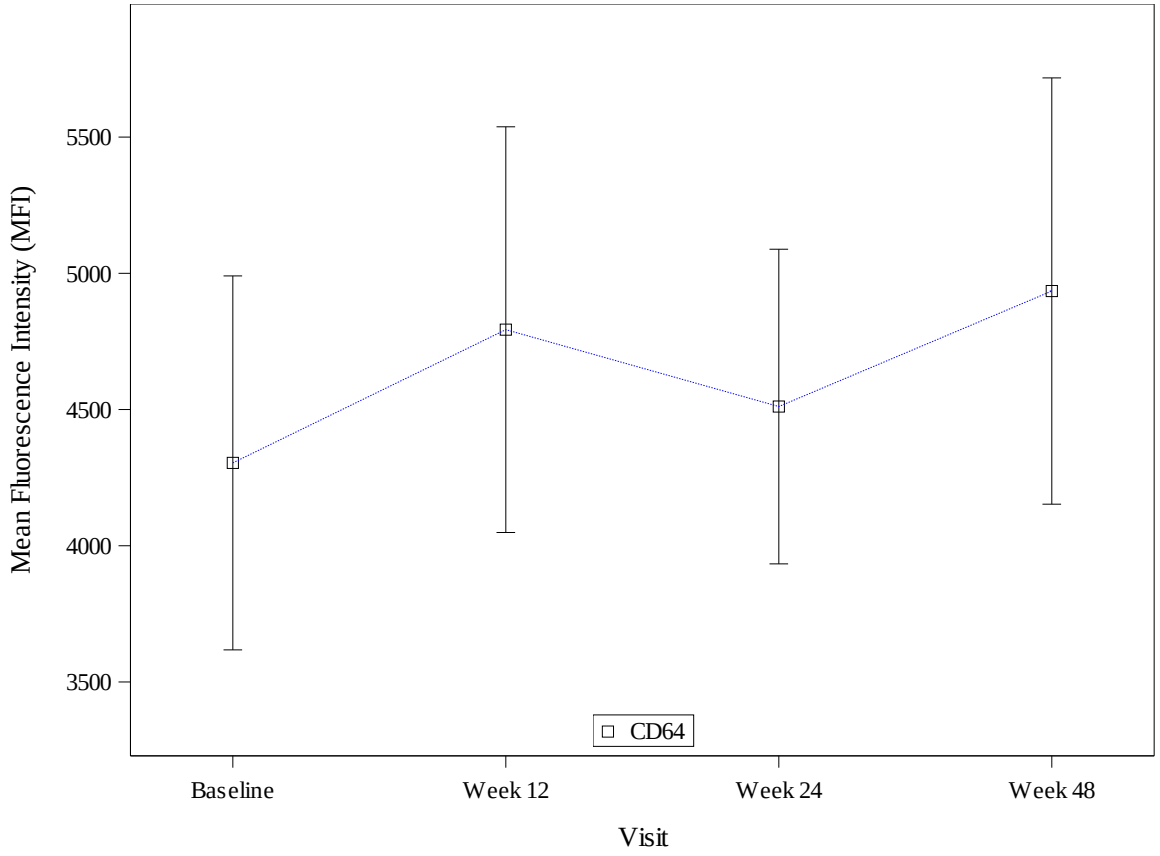
*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:08:57:46.)

For CD64, there is statistically significant difference in Week 12 and Week 48 compared to baseline.

Table 13b: Results for Primary Outcome – CD64 (Change from Baseline)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	1032.28 (340.47)	(306.58, 1757.98)	-
	Baseline CD64	-0.12 (0.07)	(-0.27, 0.03)	-
	Visit (Week 12)	-	-	498.80 (176.52, 821.08)
	Visit (Week 24)	-269.61 (215.79)	(-710.31, 171.08)	229.19 (-93.09, 551.47)
	Visit (Week 48)	166.74 (223.31)	(-289.32, 622.79)	665.54 (322.60, 1008.49)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:08:59:57.)

Figure 4: Graph of raw mean CD64 against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:15:01:19.)

CD11b

Table 14a: Results for Primary Outcome – CD11b

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	129891.88 (10272.84)	(108309.45, 151474.31)	-
	Visit (Baseline)	-	-	129891.88 (109247.84, 150535.92)
	Visit (Week 12)	24928.80 (15356.14)	(-5930.52, 55788.12)	154820.68 (133615.44, 176025.92)
	Visit (Week 24)	32288.53 (15356.14)	(1429.21, 63147.85)	162180.41 (140975.17, 183385.65)
	Visit (Week 48)	39859.23 (15790.05)	(8127.93, 71590.52)	169751.11 (147295.82, 192206.39)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:04:20.)

From Table 14a, you can see a statistically significant difference between CD11b at baseline and Week 24 and 48, at the 5% level. This difference is illustrated in Figure 5.

Table 14b: Results for Primary Outcome – CD11b (Change from Baseline)

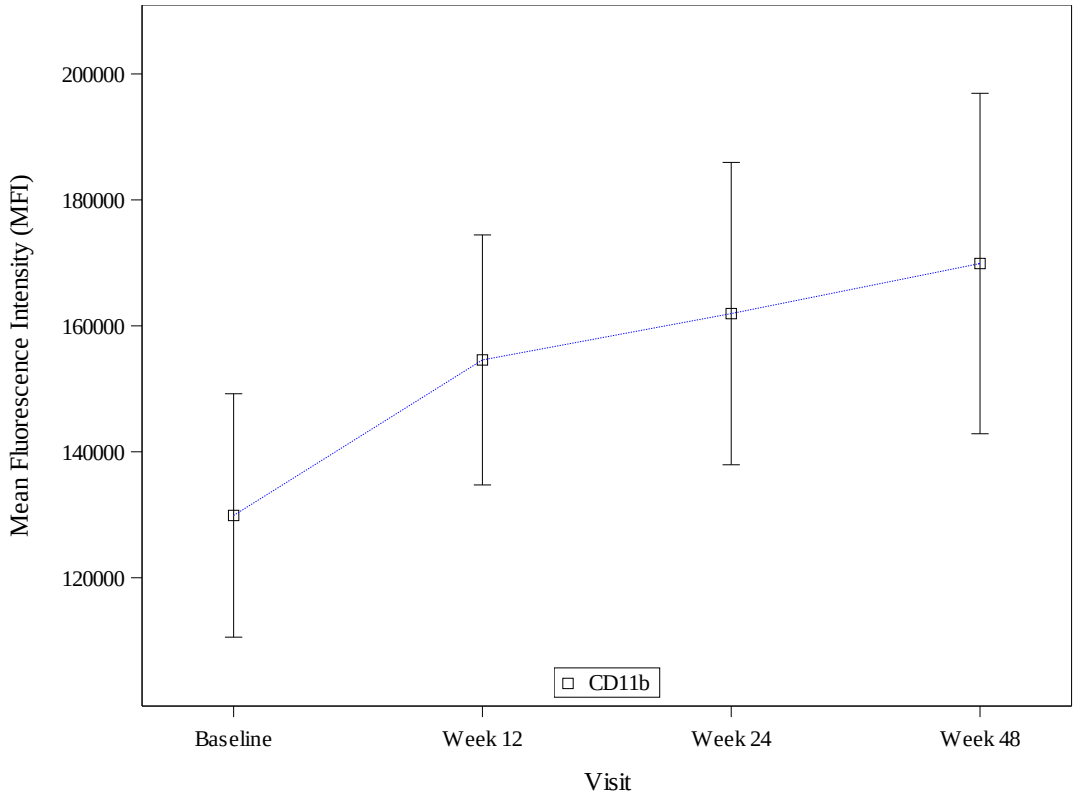
Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	154787.92 (22582.47)	(106915.22, 202660.62)	-
	Baseline CD11b	-1.00 (0.15)	(-1.32, -0.69)	-
	Visit (Week 12)	-	-	22686.17 (272.91, 45099.42)
	Visit (Week 24)	7359.73 (16638.71)	(-26532.21, 41251.67)	30045.90 (7632.65, 52459.15)
	Visit (Week 48)	15050.22 (17070.54)	(-19721.32, 49821.76)	37736.39 (14020.04, 61452.73)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:28:39.)

From Table 14b, it shows the adjustment for baseline CD11b is statistically significant.

Figure 5: Graph of raw mean CD11b against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.

*Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:15:15:19.

CD18

Table 15a: Results for Primary Outcome – CD18				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	29679.92 (5124.88)	(18912.95, 40446.88)	-
	Visit (Baseline)	-	-	29679.92 (19381.09, 39978.74)
	Visit (Week 12)	3562.01 (4342.15)	(-5163.88, 12287.89)	33241.92 (22781.72, 43702.13)
	Visit (Week 24)	1010.30 (4342.15)	(-7715.58, 9736.19)	30690.22 (20230.01, 41150.42)
	Visit (Week 48)	9920.42 (4514.53)	(848.13, 18992.72)	39600.34 (28849.46, 50351.22)

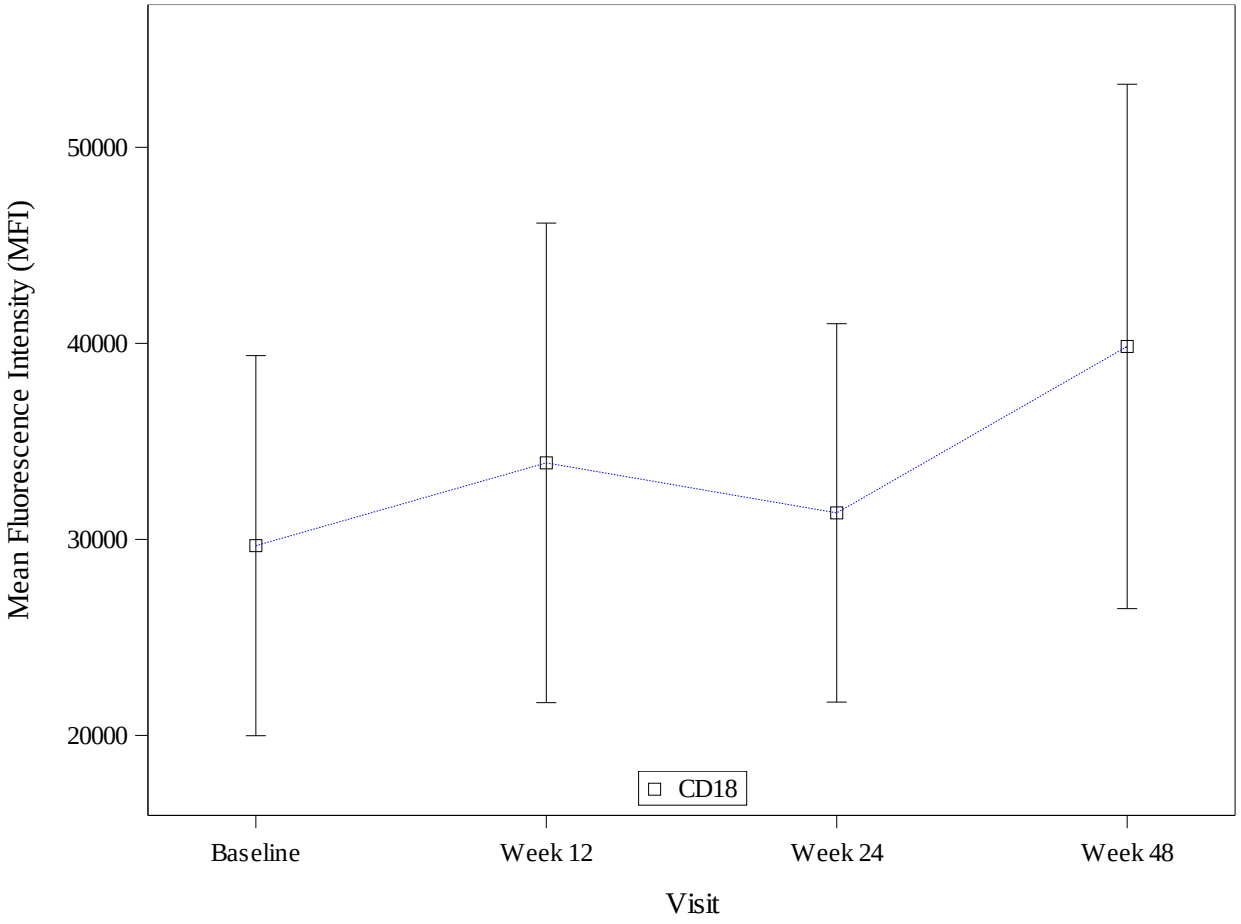
*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:36:46.)

Table 15a, shows that Week 48 CD18 shows a statistically significant difference compared to baseline.

Table 15b: Results for Primary Outcome – CD18 (Change from Baseline)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	10926.23 (6810.85)	(-3512.11, 25364.58)	-
	Baseline CD18	-0.25 (0.17)	(-0.62, 0.12)	-
	Visit (Week 12)	-	-	3261.61 (-5351.72, 11874.93)
	Visit (Week 24)	-2551.71 (4414.69)	(-11544.14, 6440.73)	709.90 (-7903.43, 9323.23)
	Visit (Week 48)	6382.19 (4592.38)	(-2972.17, 15736.56)	9643.80 (653.81, 18633.79)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:49:12.)

Figure 6: Graph of raw mean CD18 against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.
*Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:15:22:19.

CD62L

Table 16a: Results for Primary Outcome – CD62L

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	30792.45 (7131.89)	(15808.91, 45776.00)	-
	Visit (Baseline)	-	-	30792.45 (16460.38, 45124.52)
	Visit (Week 12)	-1685.93 (10256.64)	(-22297.43, 18925.56)	29106.52 (14381.73, 43831.30)
	Visit (Week 24)	-6430.41 (10256.64)	(-27041.91, 14181.08)	24362.04 (9637.26, 39086.83)
	Visit (Week 48)	11116.46 (10578.71)	(-10142.25, 32375.18)	41908.92 (26291.03, 57526.80)

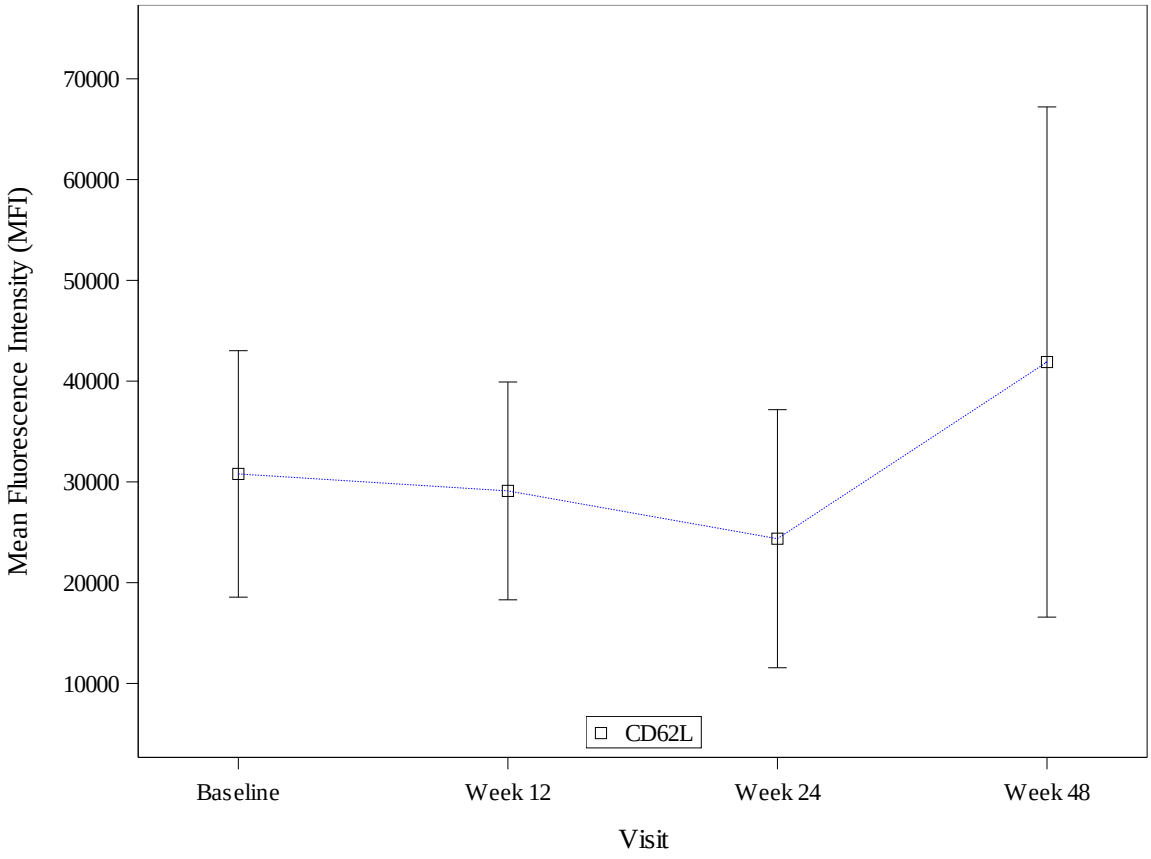
*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:51:25)

Table 16b: Results for Primary Outcome – CD62L (Change from Baseline)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	26351.35 (9371.14)	(6485.42, 46217.28)	-
	Baseline CD62L	-0.91 (0.17)	(-1.27, -0.55)	-
	Visit (Week 12)	-	-	-1855.81 (-17771.96, 14060.34)
	Visit (Week 24)	-4744.48 (11350.90)	(-27865.50, 18376.54)	-6600.29 (-22516.44, 9315.86)
	Visit (Week 48)	12735.14 (11681.80)	(-11059.91, 36530.19)	10879.33 (-5998.37, 27757.03)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:53:43.)

Table 16b, shows that the baseline adjustment of CD62L is statistically significant, at the 5% level.

Figure 7: Graph of raw mean CD62L against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.
*Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:15:35:26.

CD63

Table 17a: Results for Primary Outcome – CD63				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	14888.85 (4937.52)	(4515.52, 25262.19)	-
	Visit (Baseline)	-	-	14888.85 (4966.54, 24811.16)
	Visit (Week 12)	9417.32 (5298.25)	(-1229.90, 20064.54)	24306.17 (14165.59, 34446.75)
	Visit (Week 24)	5969.91 (5298.25)	(-4677.31, 16617.13)	20858.76 (10718.18, 30999.34)
	Visit (Week 48)	13314.37 (5501.98)	(2257.74, 24371.01)	28203.22 (17633.59, 38772.86)

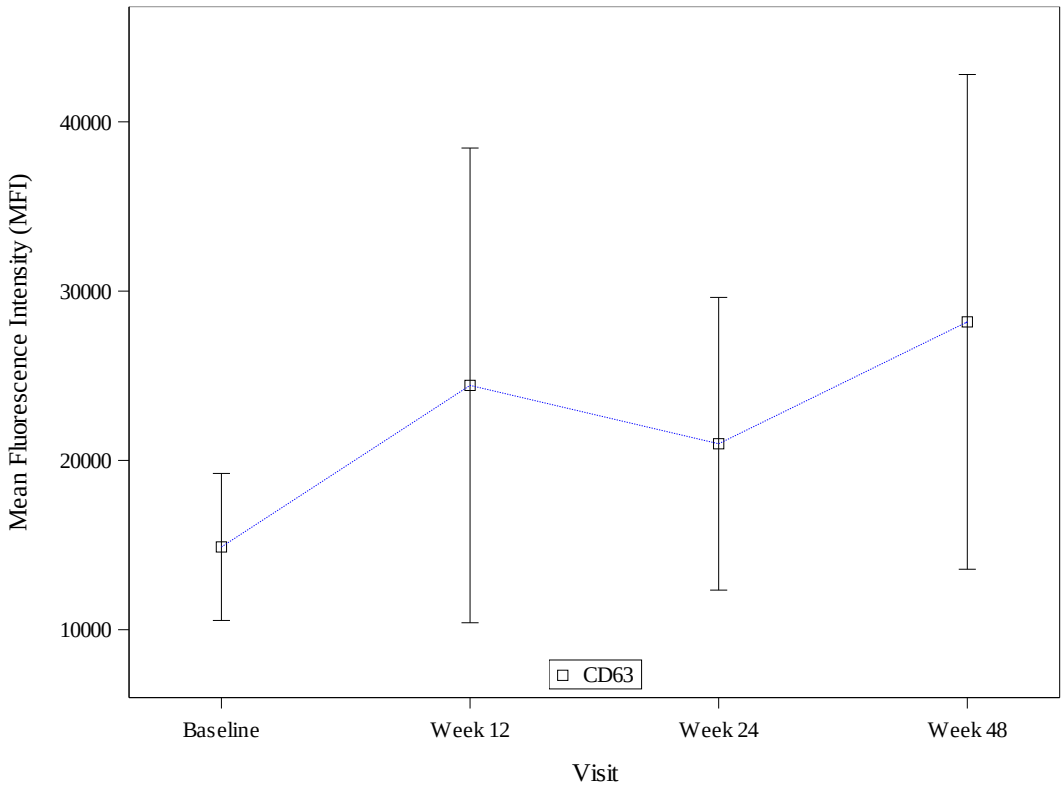
*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:55:04)

From Table 17a, there is a statistically significant difference in Week 48 compared to CD63 at baseline. This is at the 5% level.

Table 17b: Results for Primary Outcome – CD63 (Change from Baseline)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	11623.32 (9959.24)	(-9489.31, 32735.96)	-
	Baseline CD63	-0.16 (0.54)	(-1.30, 0.99)	-
	Visit (Week 12)	-	-	9283.90 (-2182.41, 20750.21)
	Visit (Week 24)	-3447.41 (5188.85)	(-14016.76, 7121.93)	5836.49 (-5629.82, 17302.80)
	Visit (Week 48)	3912.61 (5406.11)	(-7099.26, 14924.49)	13196.52 (1322.90, 25070.13)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:56:12.)

Figure 8: Graph of raw mean CD63 against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.
*Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:15:41:37.

CD66b

Table 18a: Results for Primary Outcome – CD66b

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	111592.19 (9124.38)	(92422.58, 130761.80)	-
	Visit (Baseline)	-	-	111592.19 (93256.06, 129928.32)
	Visit (Week 12)	13761.36 (12438.08)	(-11233.89, 38756.61)	125353.55 (106519.77, 144187.33)
	Visit (Week 24)	26064.73 (12438.08)	(1069.48, 51059.99)	137656.92 (118823.14, 156490.70)
	Visit (Week 48)	12506.55 (12861.73)	(-13340.07, 38353.16)	124098.73 (104148.89, 144048.58)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:09:57:36.)

Table 18a, shows a statistically significant difference at week 24, compared to baseline.

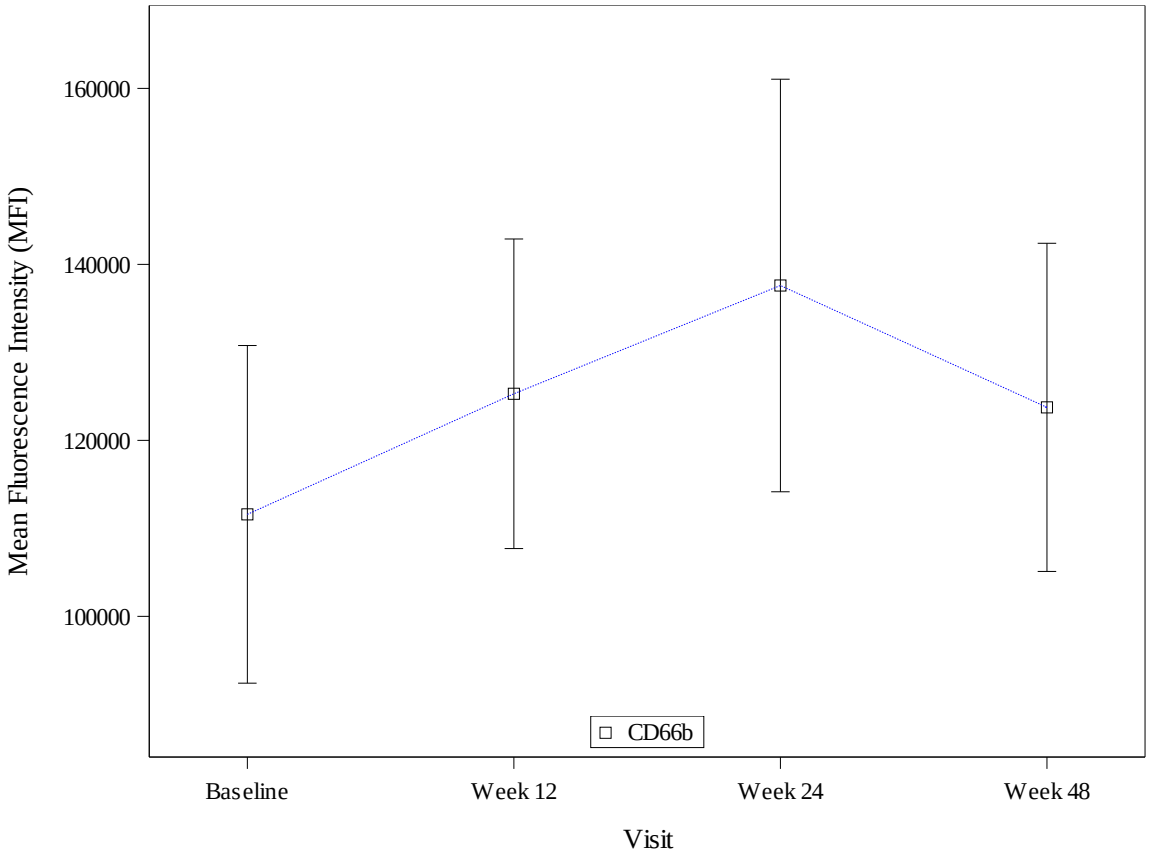
Table 18b: Results for Primary Outcome – CD66b (Change from Baseline)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	128833.13 (22103.06)	(81976.74, 175689.53)	-
	Baseline CD66b	-1.03 (0.18)	(-1.41, -0.65)	-
	Visit (Week 12)	-	-	13730.74 (-5867.28, 33328.76)
	Visit (Week 24)	12303.37 (11250.75)	(-10613.65, 35220.39)	26034.11 (6436.09, 45632.13)
	Visit (Week 48)	-237.98 (11679.85)	(-24029.05, 23553.09)	13492.76 (-7117.23, 34102.75)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:10:01:51.)

Table 18b, shows that the adjustment for baseline CD66b is statistically significant at the 5% level.

Figure 9: Graph of raw mean CD66b against time for Secukinumab



Graph shows the raw mean and 95% confidence interval.

*Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29OCT19:15:48:39.

Results for the longitudinal analysis of the change in receptor over time compared to baseline, adjusted for sex or age.

Table 19: MFI Change in Receptor Over Time from Baseline, Adjusted for either Sex or Age

Adjustment covariate	Longitudinal Model	Outcome: MFI change from baseline in surface receptor: CD16		CD64		CD11b		CD18		CD62L		CD63		CD66b	
		Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI
Sex	Intercept	78911.10 (35838.91)	(2522.27, 155299.92)	1113.64 (435.20)	(180.23, 2047.06)	156029.85 (22960.41)	(107090.89, 204968.80)	12540.06 (8220.79)	(-4982.13, 30062.25)	18263.43 (9079.40)	(-1088.84, 37615.70)	16208.73 (11408.54)	(-8108.01, 40525.46)	125598.69 (23888.93)	(74680.64, 176516.74)
	Sex (Female)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Sex (Male)	31458.04 (25387.84)	(-22654.86, 85570.95)	-70.44 (223.49)	(-549.79, 408.91)	-7560.23 (11411.02)	(-31882.23, 16761.78)	-2621.12 (7064.56)	(-17678.87, 12436.63)	20482.43 (7315.06)	(4890.74, 36074.11)	-8193.67 (9690.68)	(-28848.87, 12461.54)	6724.80 (14792.28)	(-24804.21, 38253.80)
	Baseline receptor	-0.49(0.12)	(-0.74, -0.24)	-0.13 (0.08)	(-0.31, 0.04)	-0.98 (0.15)	(-1.31, -0.65)	-0.26 (0.18)	(-0.65, 0.12)	-0.98 (0.14)	(-1.28, -0.68)	-0.19 (0.55)	(-1.35, 0.98)	-1.03 (0.18)	(-1.43, -0.64)
	Visit (Week 12)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Visit (Week 24)	-44427.58 (16469.98)	(-77975.83, -10879.34)	-269.61 (215.74)	(-710.22, 171.00)	7359.73 (16656.08)	(-26567.60, 41287.07)	-2551.71 (4416.67)	(-11548.18, 6444.76)	-4744.48 (11434.55)	(-28035.89, 18546.94)	-3447.41 (5189.84)	(-14018.77, 7123.95)	12303.37 (11224.56)	(-10560.31, 35167.05)
	Visit (Week 48)	-39753.33 (17155.55)	(-74698.04, -4808.62)	162.45 (223.65)	(-294.30, 619.19)	14496.77 (17115.95)	(-20367.29, 49360.83)	6321.77 (4598.48)	(-3045.02, 15688.56)	14750.62 (11736.15)	(-9155.14, 38656.37)	3771.27 (5409.99)	(-7248.51, 14791.06)	42.39 (11666.20)	(-23720.89, 23805.67)
Age	Intercept	73727.68 (59495.18)	(-53083.29, 200538.65)	590.29 (398.15)	(-263.67, 1444.24)	149222.18 (29611.29)	(86107.20, 212337.16)	7850.17 (14319.99)	(-22672.17, 38372.50)	31909.54 (20477.83)	(-11737.92, 75557.00)	12525.55 (21020.18)	(-32277.90, 57329.00)	140278.67 (29016.57)	(78431.31, 202126.03)
	Age	357.99 (974.79)	(-1719.72, 2435.70)	15.11 (8.14)	(-2.35, 32.56)	121.62 (415.52)	(-764.04, 1007.28)	63.33 (257.66)	(-485.85, 612.52)	-105.22 (342.61)	(-835.47, 625.04)	-17.99 (365.53)	(-797.09, 761.10)	-387.48 (621.83)	(-1712.89, 937.93)
	Baseline Receptor	-0.47 (0.12)	(-0.74, -0.21)	-0.20 (0.08)	(-0.36, -0.03)	-1.00 (0.15)	(-1.33, -0.68)	-0.25 (0.18)	(-0.63, 0.13)	-0.93 (0.18)	(-1.31, -0.54)	-0.16 (0.56)	(-1.35, 1.04)	-0.97 (0.21)	(-1.42, -0.52)
	Visit (Week 12)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Visit (Week 24)	-44427.58 (16441.75)	(-77918.32, -10936.84)	-269.61 (215.47)	(-709.67, 170.44)	7359.73 (16652.62)	(-26560.55, 41280.01)	-2551.71 (4416.13)	(-11547.07, 6443.66)	-4744.48 (11360.17)	(-27884.38, 18395.43)	-3447.41 (5190.03)	(-14019.16, 7124.34)	12303.37 (11235.36)	(-10582.32 ,35189.06)
	Visit (Week 48)	-40700.80 (17130.35)	(-75594.17, -5807.42)	149.19 (222.91)	(-306.06, 604.44)	14867.11 (17111.55)	(-19987.98, 49722.20)	6352.55 (4596.74)	(-3010.70, 15715.80)	12891.33 (11711.06)	(-10963.32, 36745.99)	3913.59 (5409.79)	(-7105.78, 14932.97)	15.11 (11671.68)	(-23759.33, 23789.54)

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:10:03:58.)

From Table 19, it can be seen that the statistically significant differences seen in previous models still hold when the models are adjusted from by sex or age.

Tables 20-22 and Figures 10-12 give summary results for neutrophil lifespan at each study visit with and without an added cytokine.

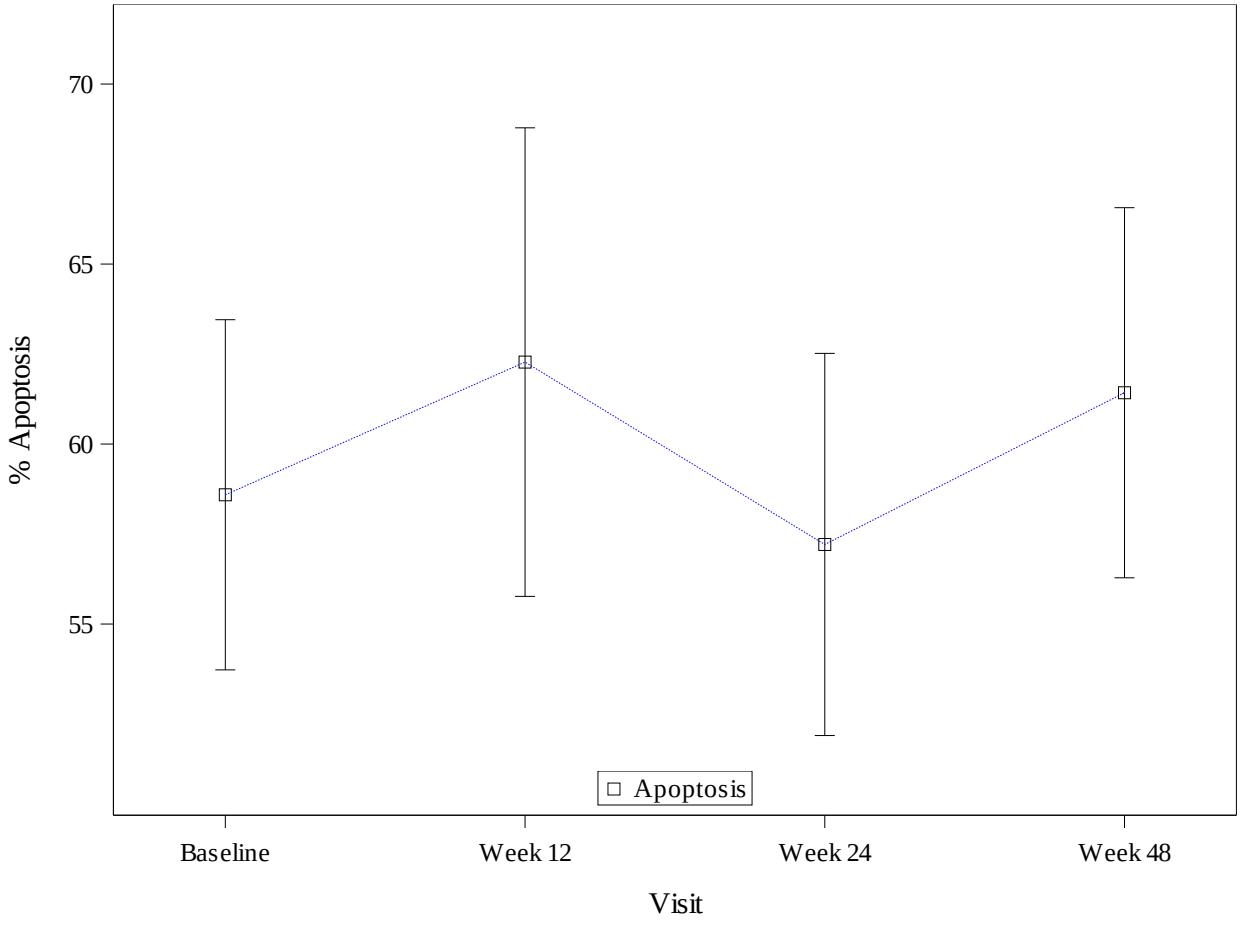
Table 20: Results for Primary Outcome – Neutrophil lifespan (% cells apoptosis)

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	58.59 (2.51)	(53.31, 63.87)	-
	Visit (Baseline)	-	-	58.59 (53.54, 63.64)
	Visit (Week 12)	3.78 (2.95)	(-2.15, 9.70)	62.37 (57.19, 67.54)
	Visit (Week 24)	-1.29 (2.95)	(-7.21, 4.64)	57.30 (52.13, 62.48)
	Visit (Week 48)	3.36 (3.06)	(-2.79, 9.51)	61.95 (56.52, 67.38)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_Apoptosis found on Statistics Server by RG on 29NOV19:10:12:32.)

Figure 10: Graph of raw mean Neutrophil lifespan for Secukinumab patients



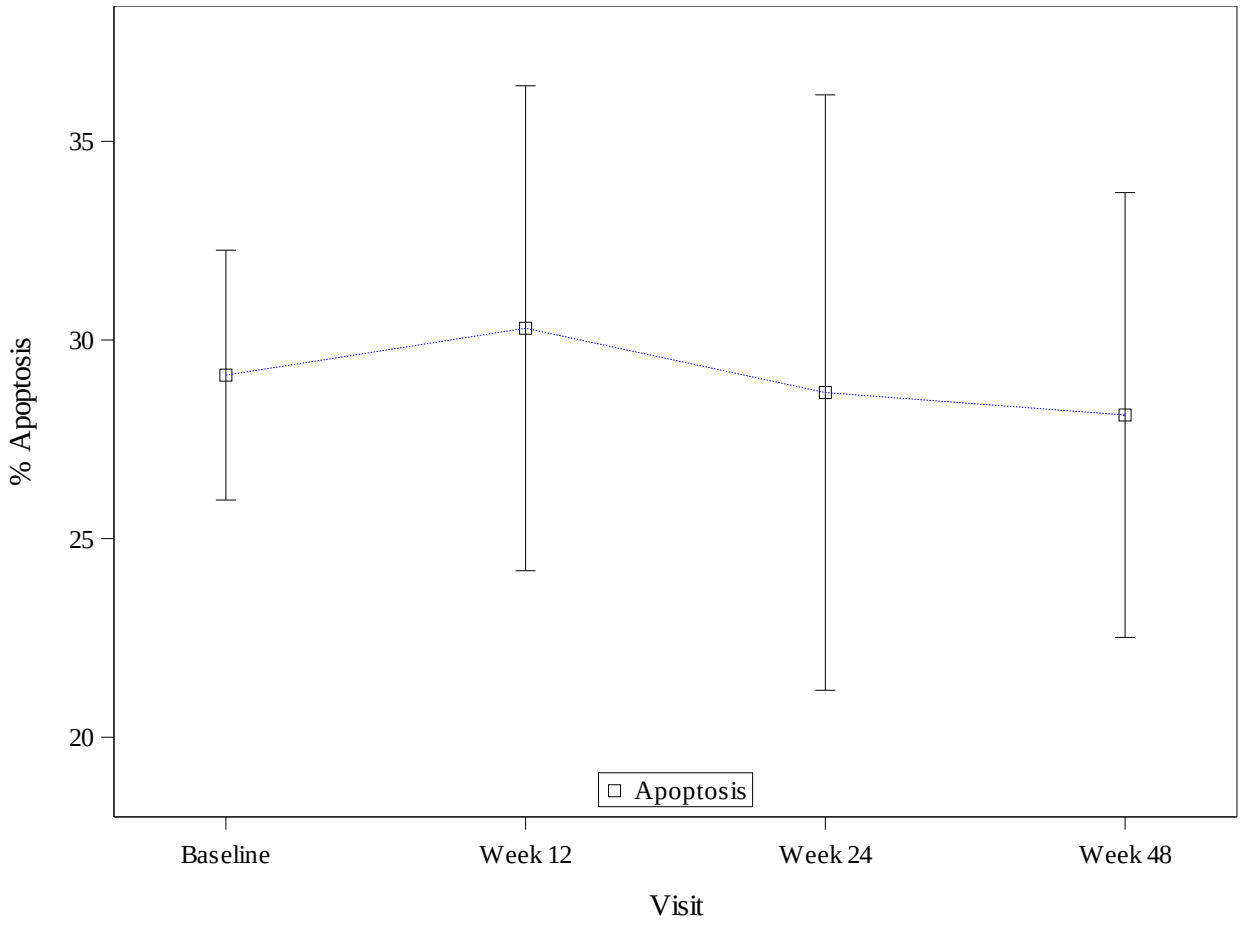
Graph shows the raw mean and 95% confidence interval.

*Created using R_SATURN_Registration1 and R_SATURN_Apoptosis found on Statistics Server by RG on 01NOV19:11:57:57.

Table 21: Results for Primary Outcome – Neutrophil lifespan (% cells apoptosis) (added cytokine GMCSF)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	29.12 (2.65)	(23.55, 34.68)	-
	Visit (Baseline)	-	-	29.12 (23.80, 34.44)
	Visit (Week 12)	1.19 (3.16)	(-5.16, 7.55)	30.31 (24.85, 35.76)
	Visit (Week 24)	-0.43 (3.16)	(-6.78, 5.93)	28.69 (23.24, 34.14)
	Visit (Week 48)	-0.40 (3.28)	(-6.99, 6.19)	28.72 (22.99, 34.44)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_Apoptosis found on Statistics Server by RG on 29NOV19:10:14:32.)

Figure 11: Graph of raw mean Neutrophil lifespan for Secukinumab patients (added cytokine GMCSF)

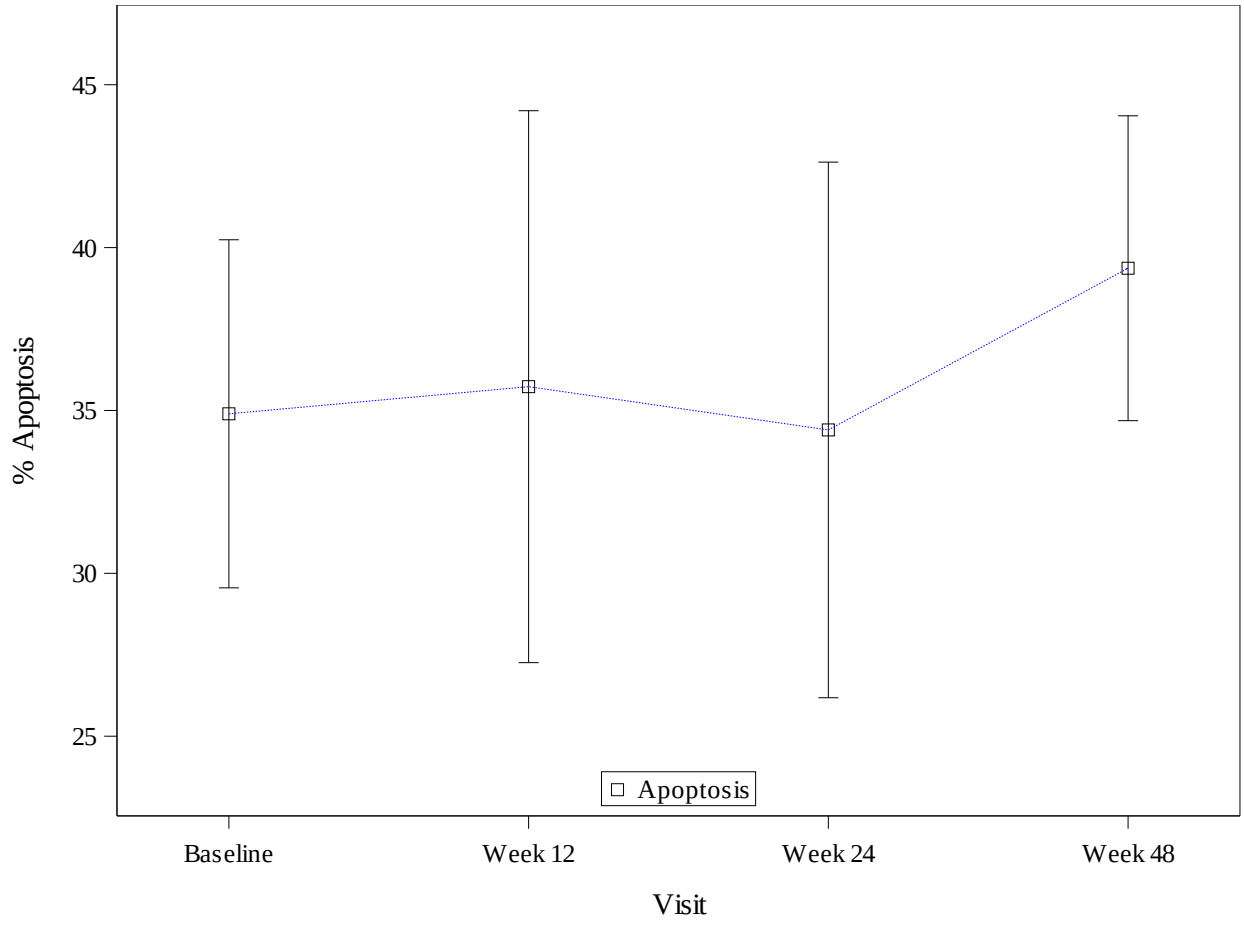


Graph shows the raw mean and 95% confidence interval.
(Created using R_SATURN_Registration1 and R_SATURN_Apoptosis found on Statistics Server by RG on 01NOV19:11:56:12.)

Table 22: Results for Primary Outcome – Neutrophil lifespan (% cells apoptosis) (added cytokine TNF)				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	34.90 (3.19)	(28.20, 41.60)	-
	Visit (Baseline)	-	-	34.90 (28.49, 41.31)
	Visit (Week 12)	0.83 (3.77)	(-6.74, 8.41)	35.73 (29.16, 42.29)
	Visit (Week 24)	-0.50 (3.77)	(-8.07, 7.08)	34.40 (27.84, 40.97)
	Visit (Week 48)	4.78 (3.91)	(-3.08, 12.63)	39.67 (32.79, 46.56)

*Least Squares Estimate
(Created using R_SATURN_Registration1 and R_SATURN_Apoptosis found on Statistics Server by RG on 29NOV19:10:16:48.)

Figure 12: Graph of raw mean Neutrophil lifespan for Secukinumab patients (added cytokine TNF)



Graph shows the raw mean and 95% confidence interval.
(Created using R_SATURN_Registration1 and R_SATURN_Apoptosis found on Statistics Server by RG on 01NOV19:12:04:32.)

8.6 Analysis of Secondary Outcomes

Table 23 and Figure 13 give summary results for vitamin D receptor for neutrophils at each study visit.

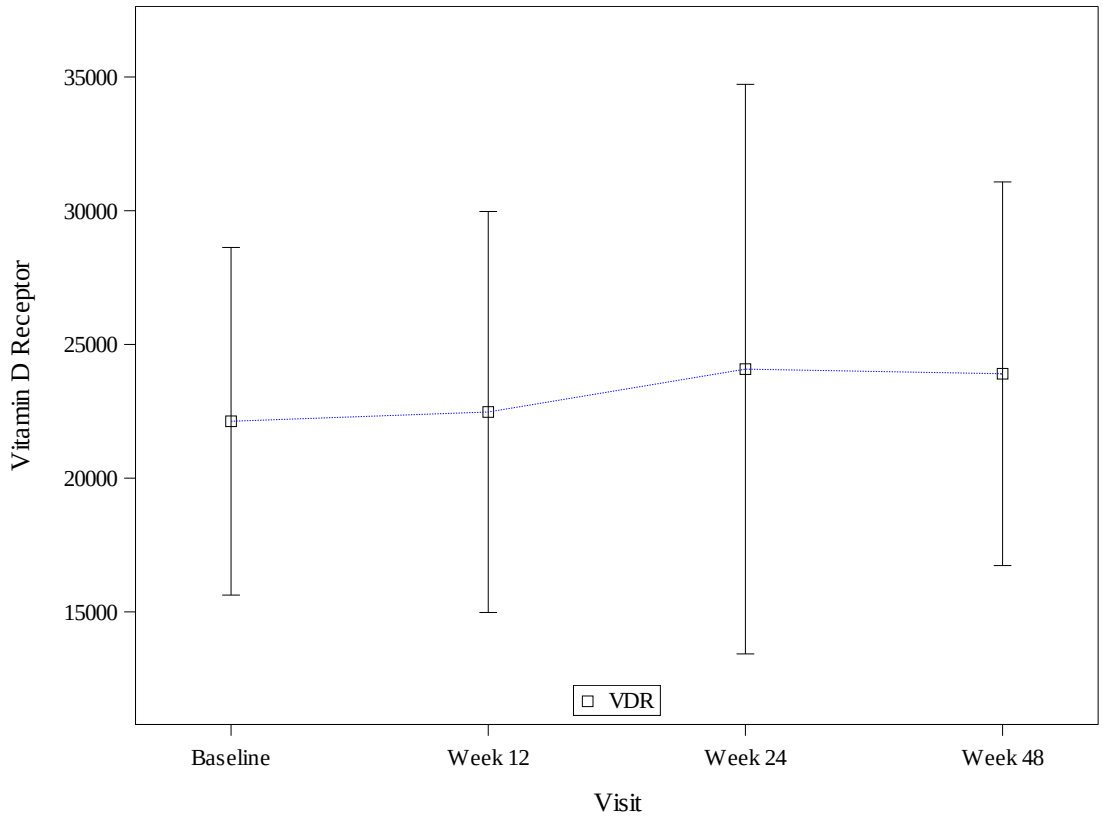
Table 23: Results for Secondary Outcome – Vitamin D Receptor (Neutrophils)

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	22126.69 (3722.21)	(14306.62, 29946.77)	-
	Visit (Baseline)	-	-	22126.69 (14646.64, 29606.75)
	Visit (Week 12)	458.60 (5671.55)	(-10938.81, 11856.01)	22585.30 (14903.87, 30266.72)
	Visit (Week 24)	2061.22 (5671.55)	(-9336.19, 13458.63)	24187.92 (16506.50, 31869.34)
	Visit (Week 48)	2054.00 (5819.03)	(-9639.77, 13747.78)	24180.70 (16066.04, 32295.35)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:10:18:11.)

Figure 13: Vitamin D Receptor for neutrophils, Secukinumab patients



Graph shows the raw mean and 95% confidence interval.

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 01NOV19:13:57:52.)

Table 24 and Figure 14 give summary results for vitamin D receptor for either monocytes or lymphocytes at each study visit.

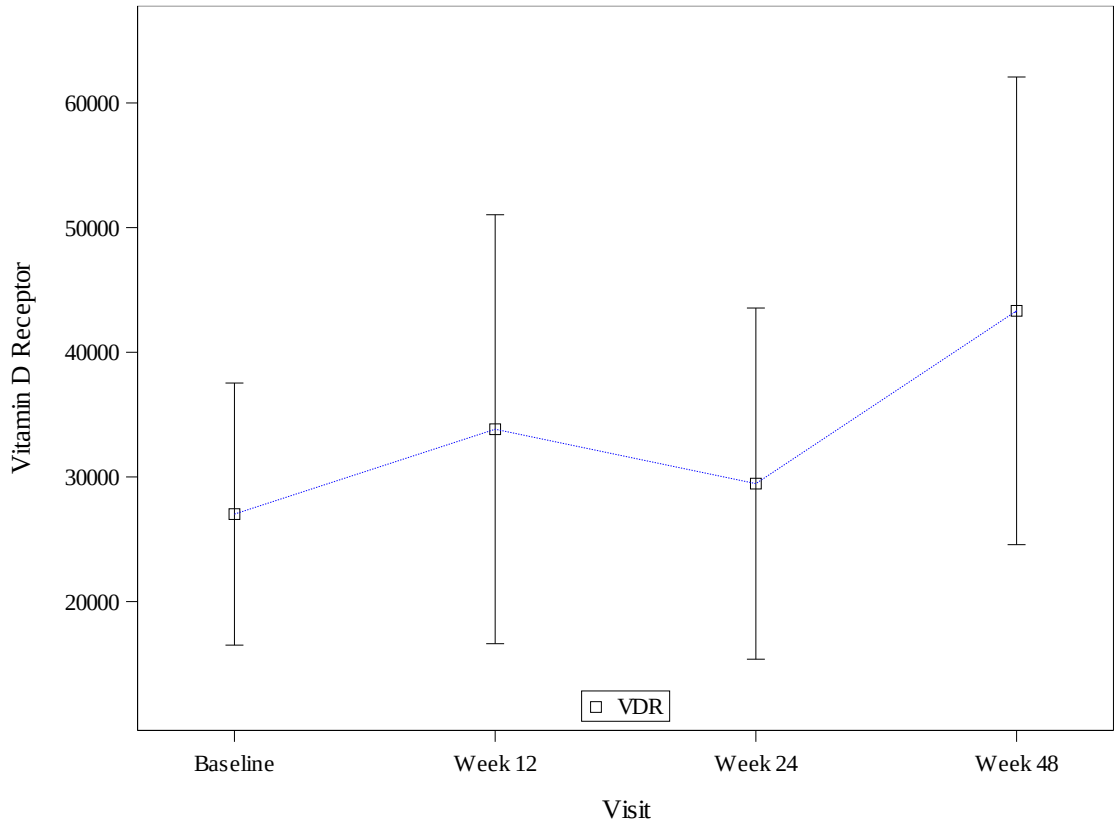
Table 24: Results for Secondary Outcome – Vitamin D Receptor (Other)

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	27020.17 (6926.08)	(12469.02, 41571.33)	-
	Visit (Baseline)	-	-	27020.17 (13101.69, 40938.66)
	Visit (Week 12)	6667.07 (9305.52)	(-12033.06, 25367.21)	33687.25 (19393.23, 47981.27)
	Visit (Week 24)	2304.26 (9305.52)	(-16395.88, 21004.39)	29324.43 (15030.41, 43618.45)
	Visit (Week 48)	15710.95 (9627.33)	(-3635.89, 35057.79)	42731.12 (27600.88, 57861.37)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 29NOV19:10:19:32.)

Figure 14: Vitamin D Receptor for other, Secukinumab patients



Graph shows the raw mean and 95% confidence interval.

(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 01NOV19:14:05:19.)

Table 25 and Figure 15 give summary results for vitamin D concentrations at each study visit. The Vitamin D concentration comes from the total Vitamin D.

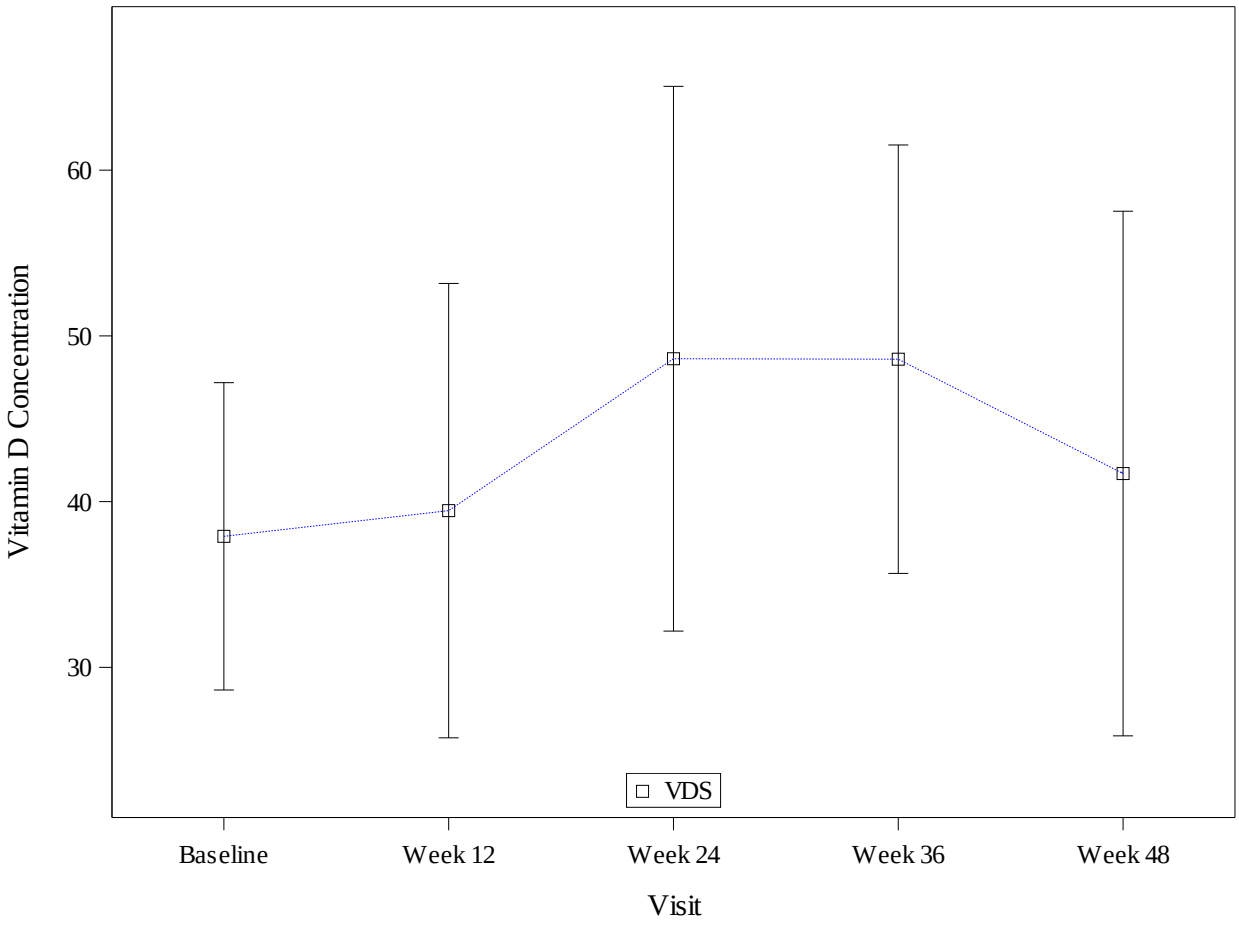
Table 25: Results for Secondary Outcome – Vitamin D Concentrations

Arm	Longitudinal Model	Estimate (Standard Error)	95% Confidence Interval	LSE* (95% Confidence Interval)
Secukinumab	Intercept	37.91 (6.22)	(24.83, 50.98)	-
	Visit (Baseline)	-	-	37.91(25.48,50.33)
	Visit (Week 12)	1.52 (5.80)	(-10.06, 13.10)	39.43(26.78,52.08)
	Visit (Week 24)	10.69 (5.80)	(-0.90, 22.27)	48.59(35.94,61.24)
	Visit (Week 36)	10.30 (5.91)	(-1.50, 22.10)	48.20(35.35,61.05)
	Visit (Week 48)	3.40 (5.91)	(-8.40, 15.20)	41.30(28.45,54.15)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_VitaminDForm found on Statistics Server by RG on 29NOV19:10:22:53.)

Figure 15: Vitamin D Concentration, Secukinumab patients



Graph shows the raw mean and 95% confidence interval.

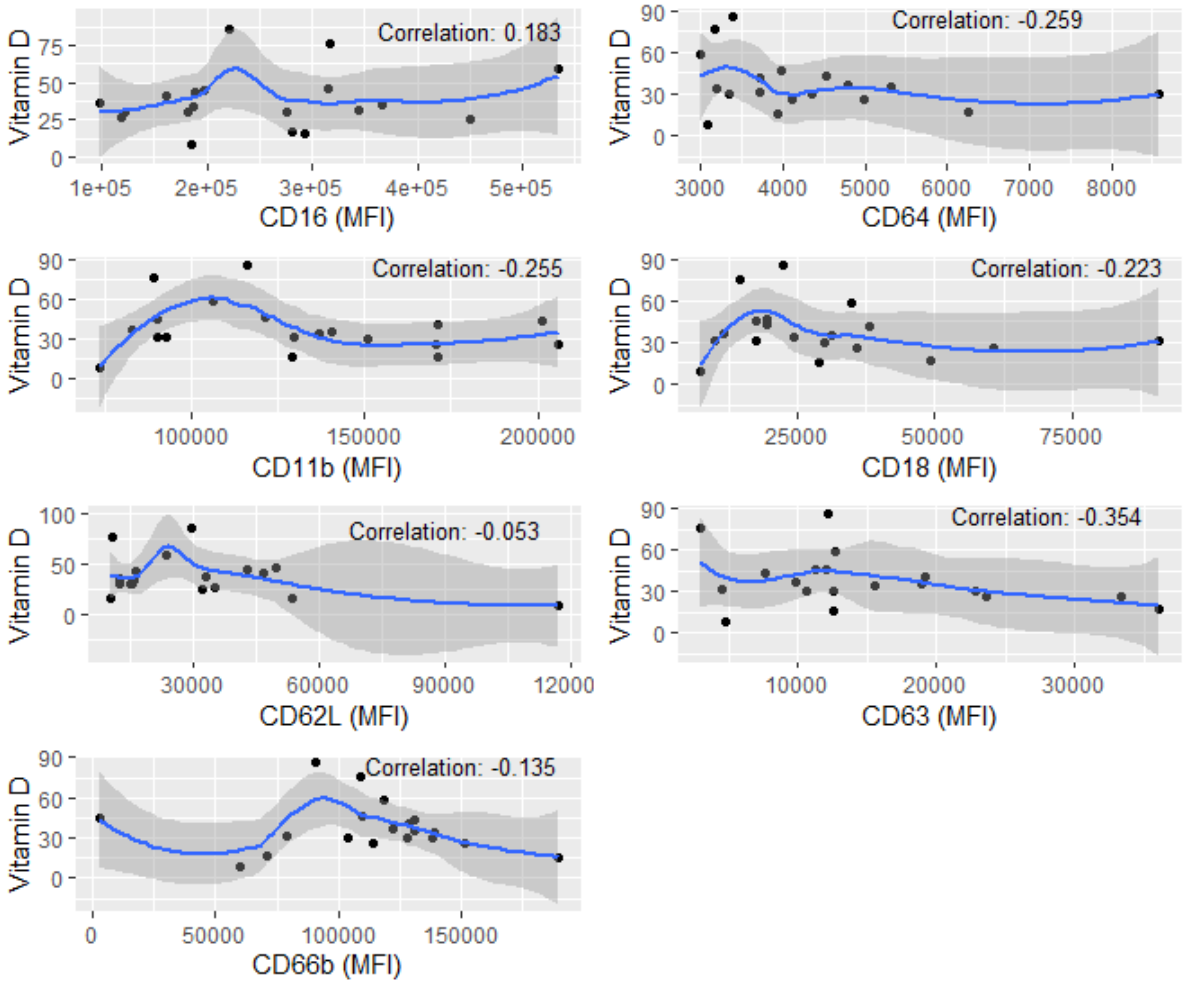
(Created using R_SATURN_Registration1 and R_SATURN_VitaminDForm found on Statistics Server by RG on 01NOV19:14:23:34.)

To determine if neutrophil life span and function is associated with vitamin D concentration and VDR receptor a series of correlation plots have been produced.

Values corresponding to the following figures were queried if outliers seemed present, however data was checked at source and deemed accurate.

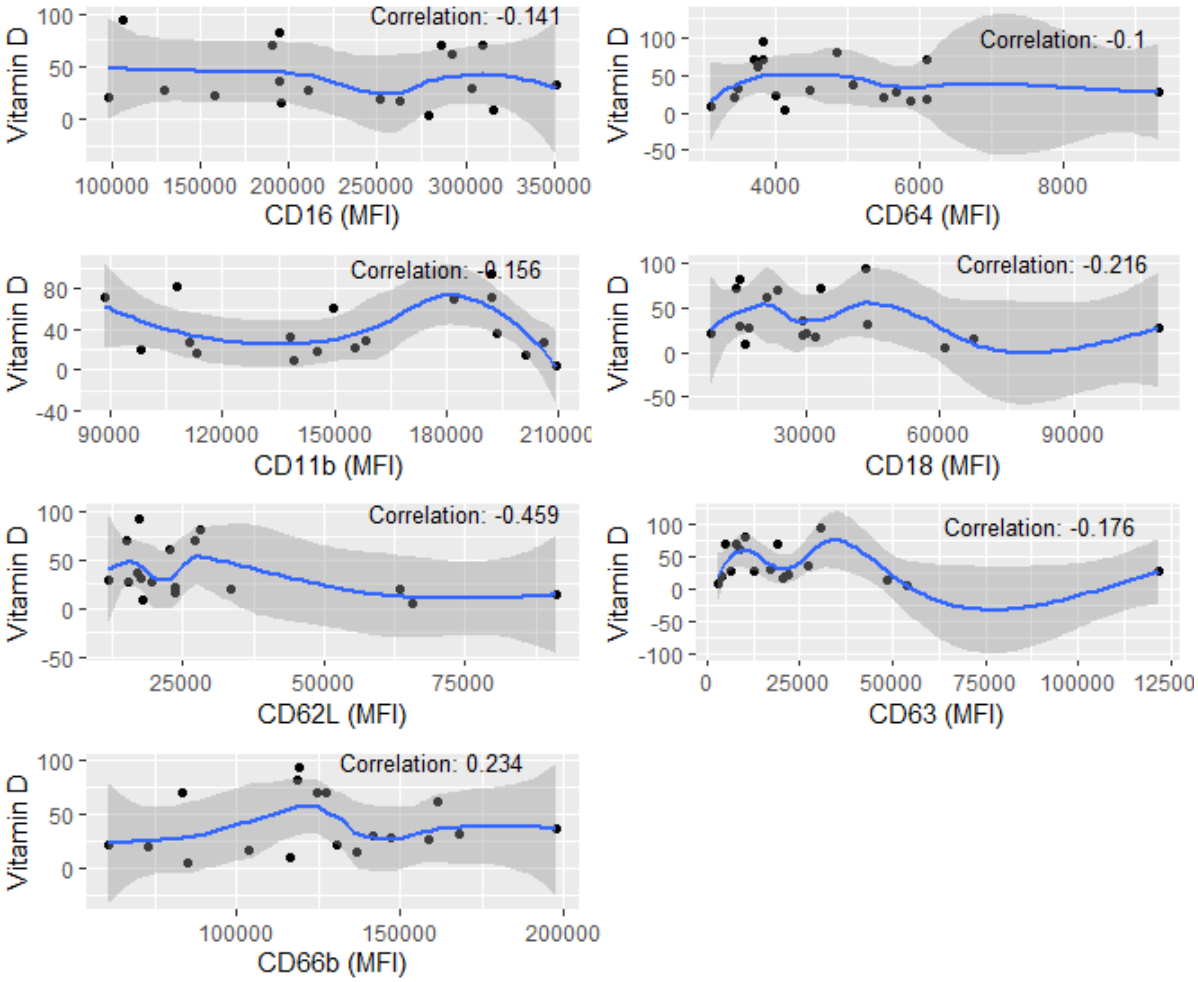
Figure 16a-16d; show a panel of correlation plots between Neutrophil phenotype and vitamin D concentration at different time points. Moving averages were used to fit the regression line and show the 95 % confidence intervals. Spearman's Correlations are presented alongside each of the figures.

Figure 16a – Panel of correlation plots between Vitamin D concentration and Neutrophil phenotype, at baseline.



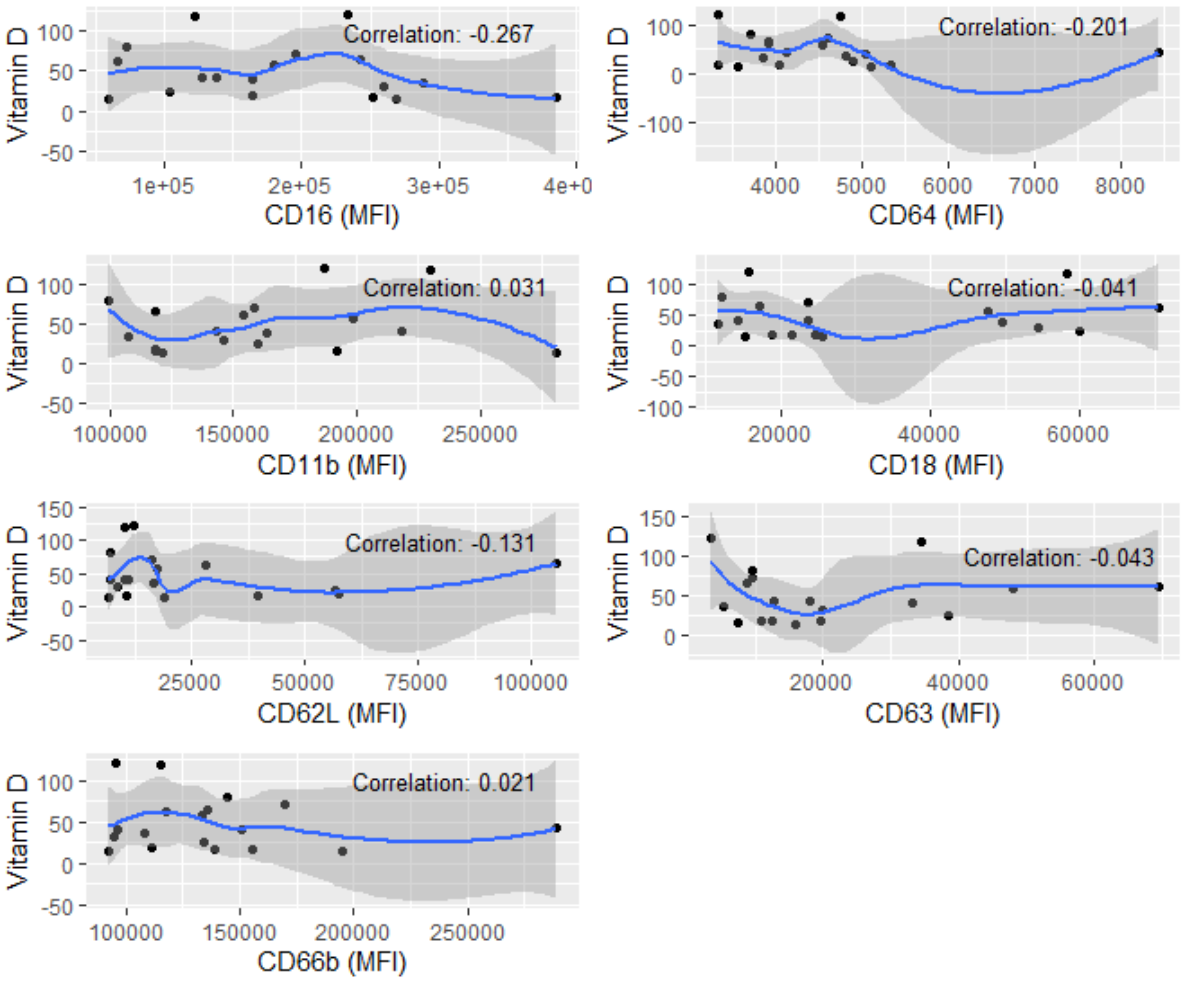
(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_VitaminDForm found on Statistics Server by RG on 11NOV19:16:50:10.)

Figure 16b – Panel of correlation plots between Vitamin D concentration and Neutrophil phenotype, at Week 12.



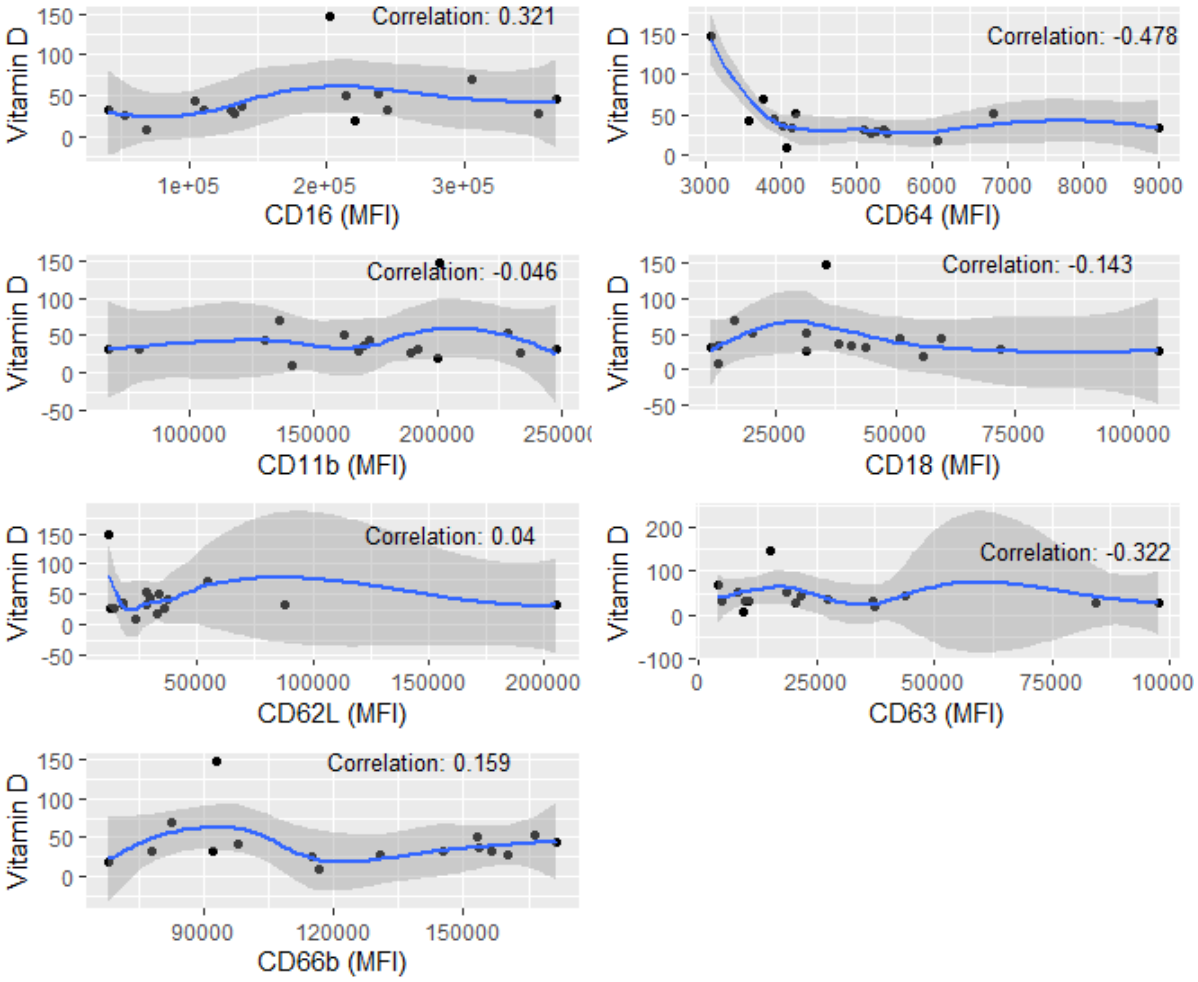
(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_VitaminDForm found on Statistics Server by RG on 11NOV19:16:50:29.)

Figure 16c – Panel of correlation plots between Vitamin D concentration and Neutrophil phenotype, at Week 24.



(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_VitaminDForm found on Statistics Server by RG on 11NOV19:16:50:49.)

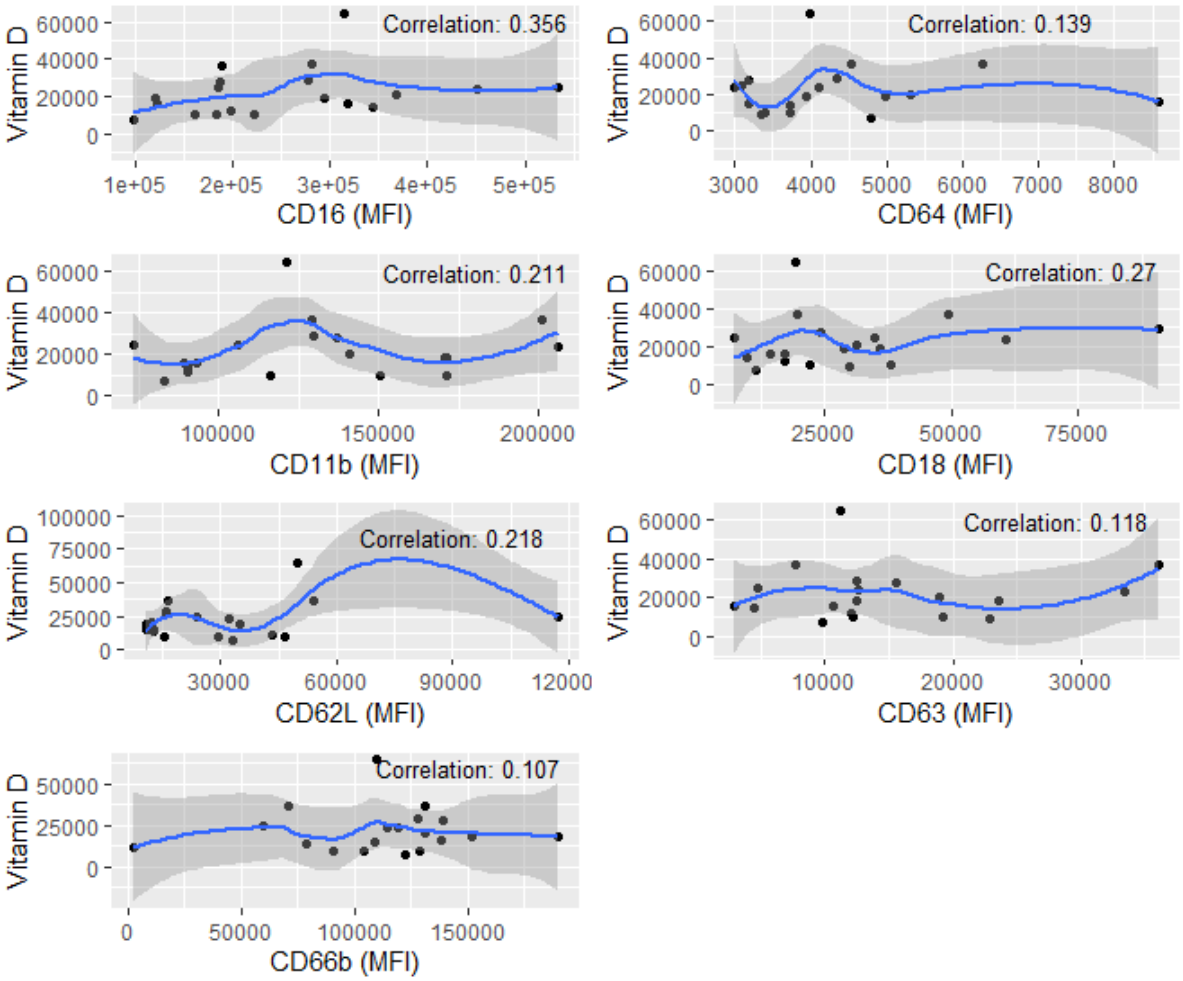
Figure 16d – Panel of correlation plots between Vitamin D concentration and Neutrophil phenotype, at Week 48.



(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_VitaminDForm found on Statistics Server by RG on 11NOV19:16:51:10.)

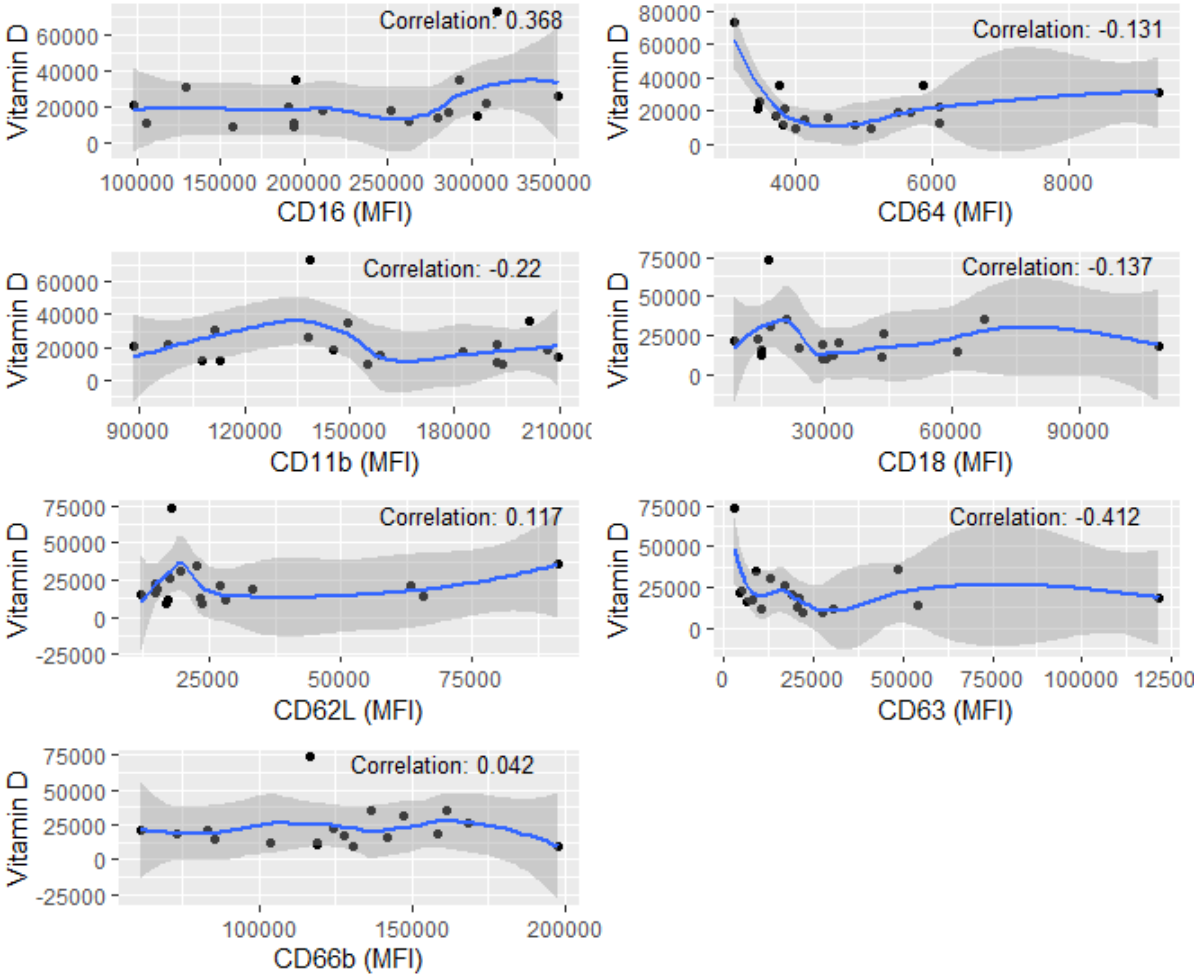
Figure 17a-17d; show a panel of correlation plots between Neutrophil phenotype and vitamin D receptor, at different time points.

Figure 17a – Panel of correlation plots between Vitamin D receptor (Neutrophil) and Neutrophil phenotype, at baseline.



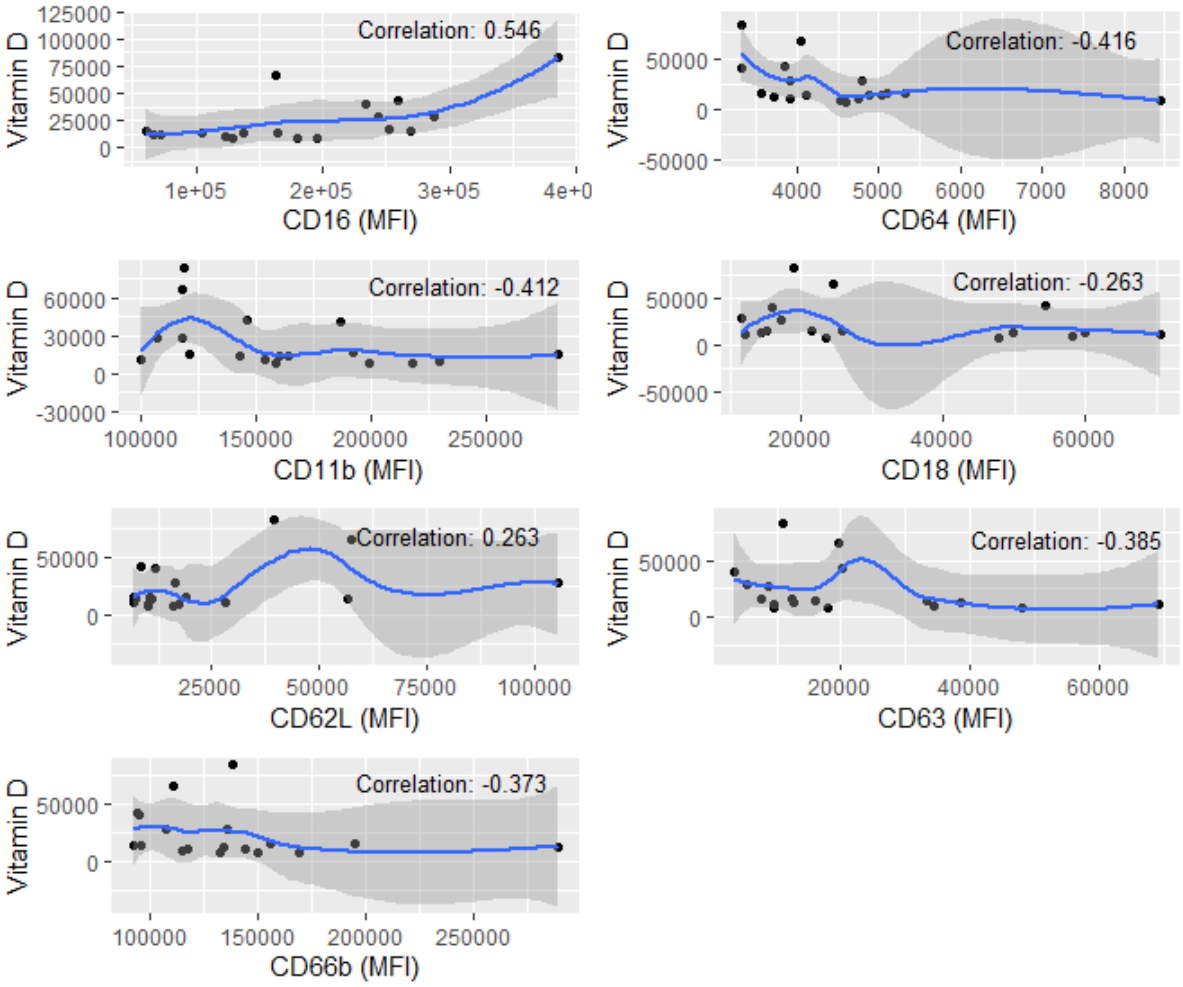
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 11NOV19:16:55:38.)

Figure 17b – Panel of correlation plots between Vitamin D receptor (Neutrophil) and Neutrophil phenotype, at Week 12.



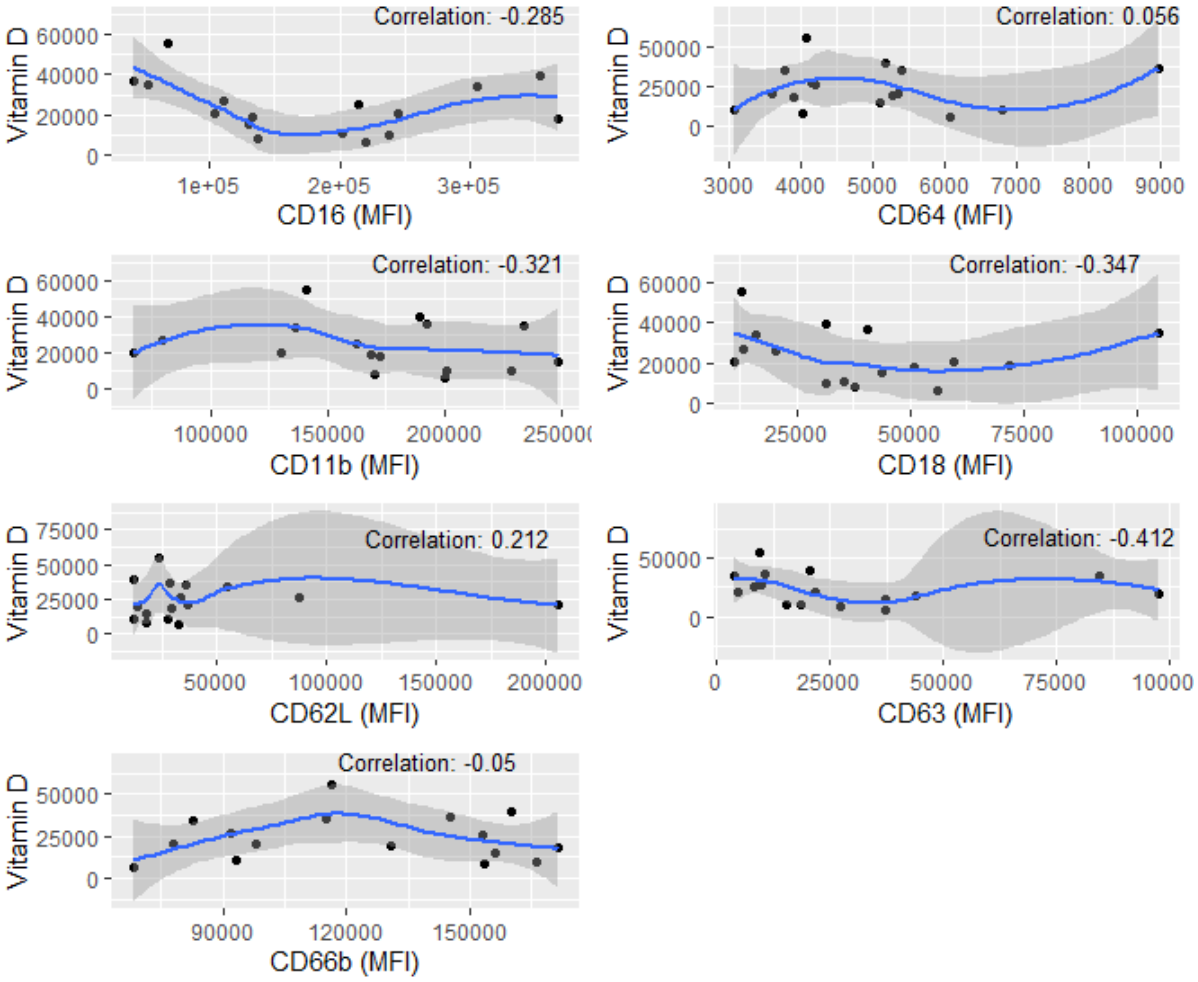
(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 11NOV19:16:55:56.)

Figure 17c – Panel of correlation plots between Vitamin D receptor (Neutrophil) and Neutrophil phenotype, at Week 24.



(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 11NOV19:16:56:12.)

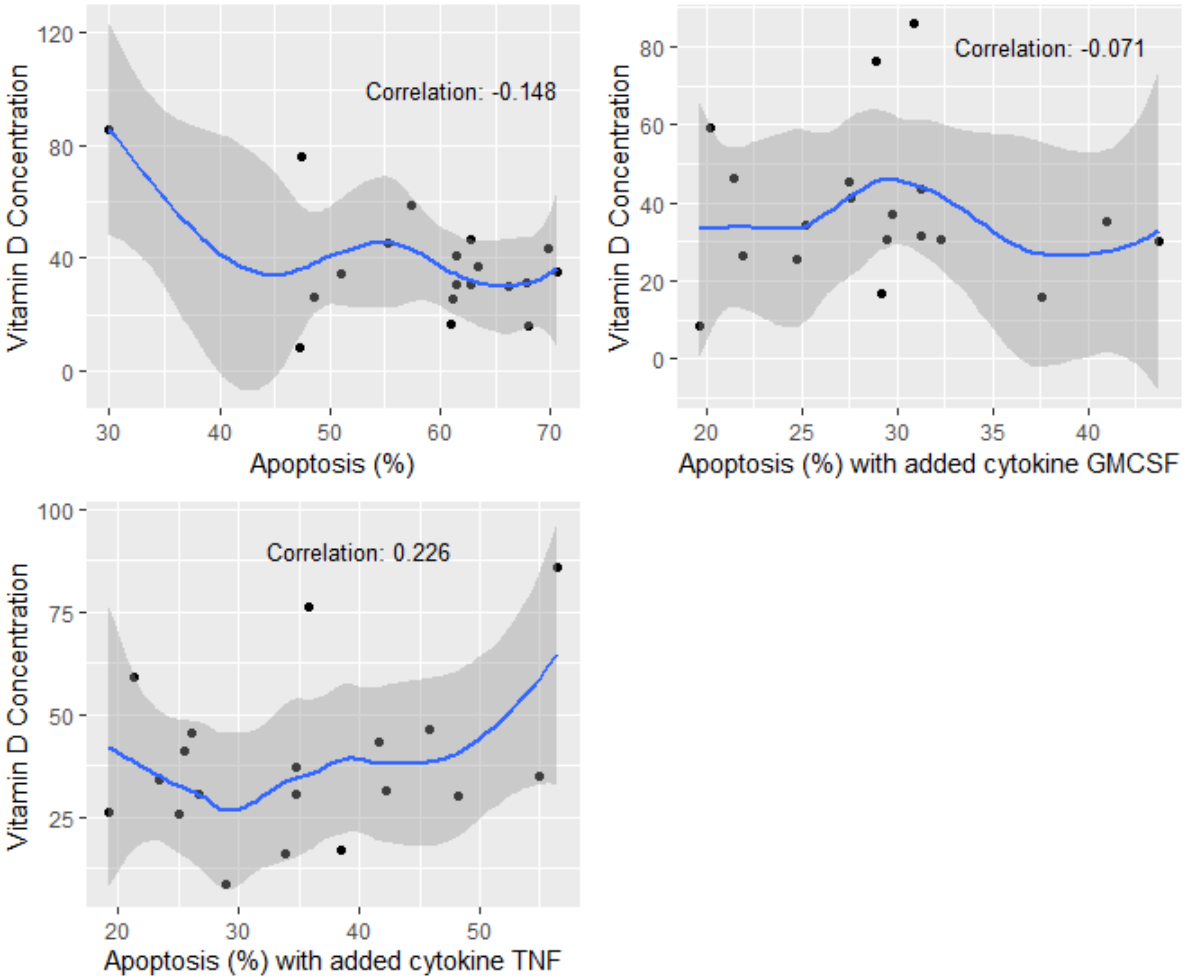
Figure 17d – Panel of correlation plots between Vitamin D receptor (Neutrophil) and Neutrophil phenotype, at Week 48.



(Created using R_SATURN_Registration1 and R_SATURN_SurfaceRec found on Statistics Server by RG on 11NOV19:16:56:29.)

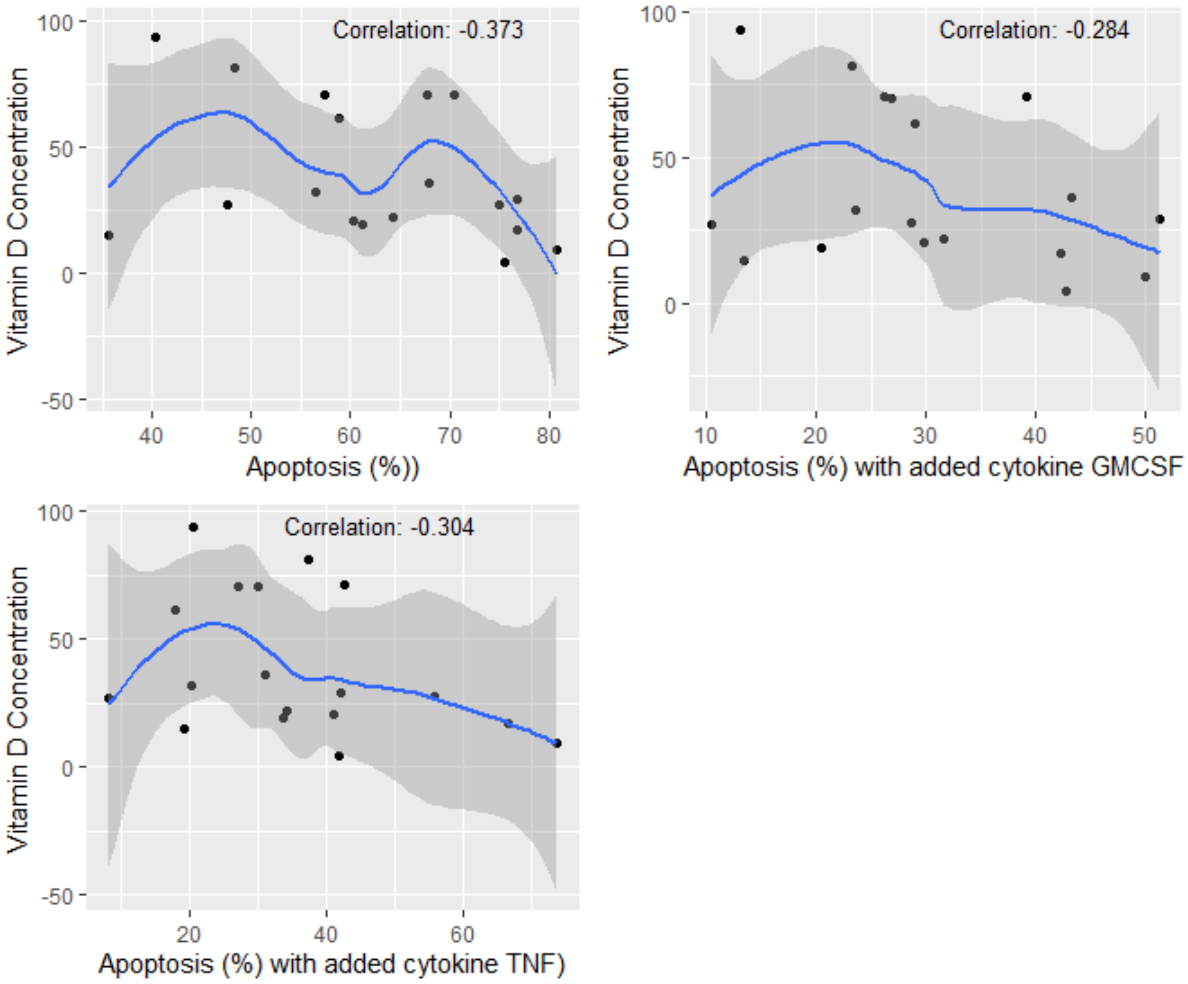
Figure 18a-18d; show a panel of correlation plots between Neutrophil apoptosis % with and without cytokines and vitamin D concentration, at different time points.

Figure 18a – Panel of correlation plots between Vitamin D concentration and Neutrophil apoptosis %, at baseline.



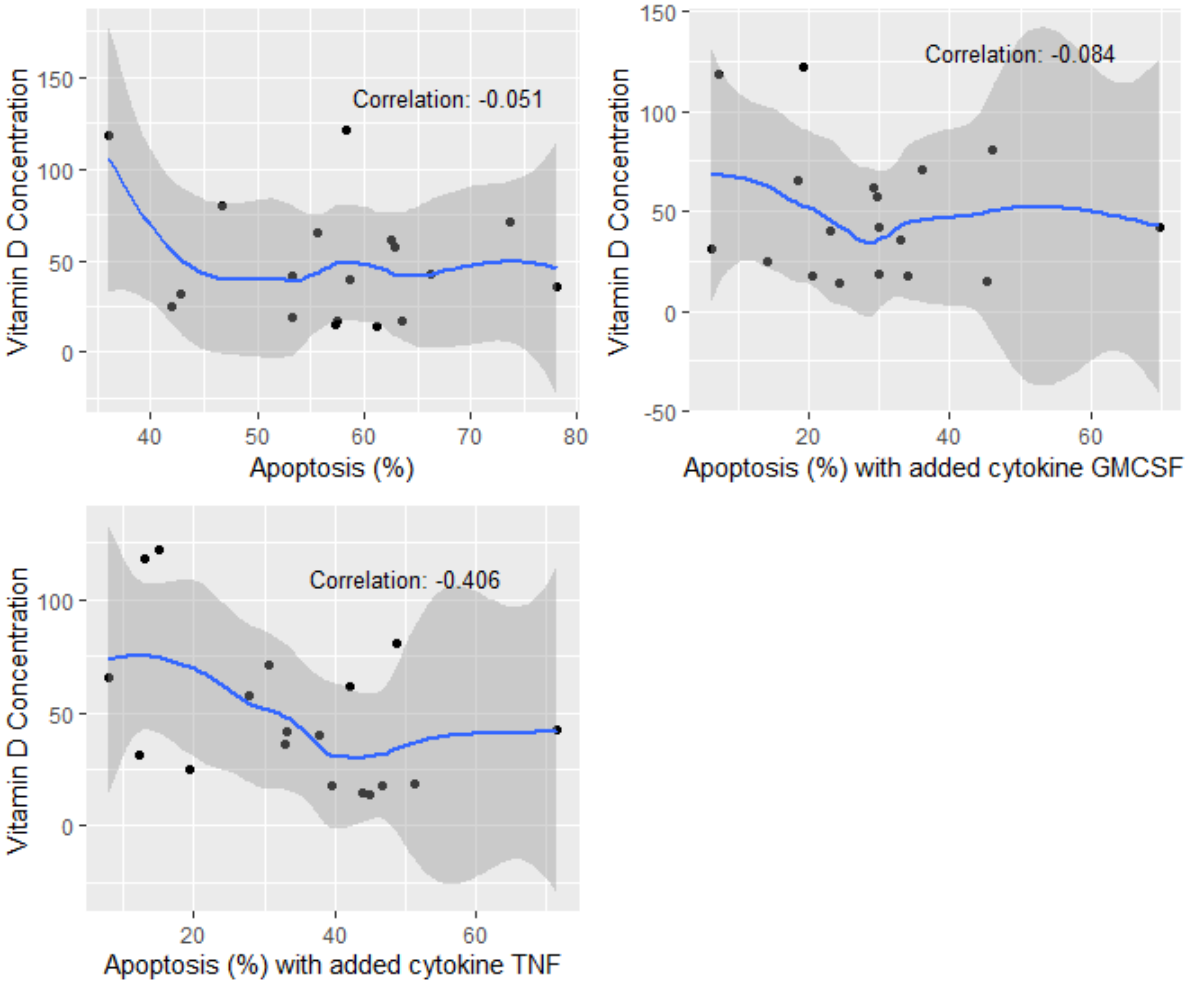
(Created using R_SATURN_Registration1, R_SATURN_VitaminDForm and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:10:10:12.)

Figure 18b – Panel of correlation plots between Vitamin D concentration and Neutrophil apoptosis %, at Week 12.



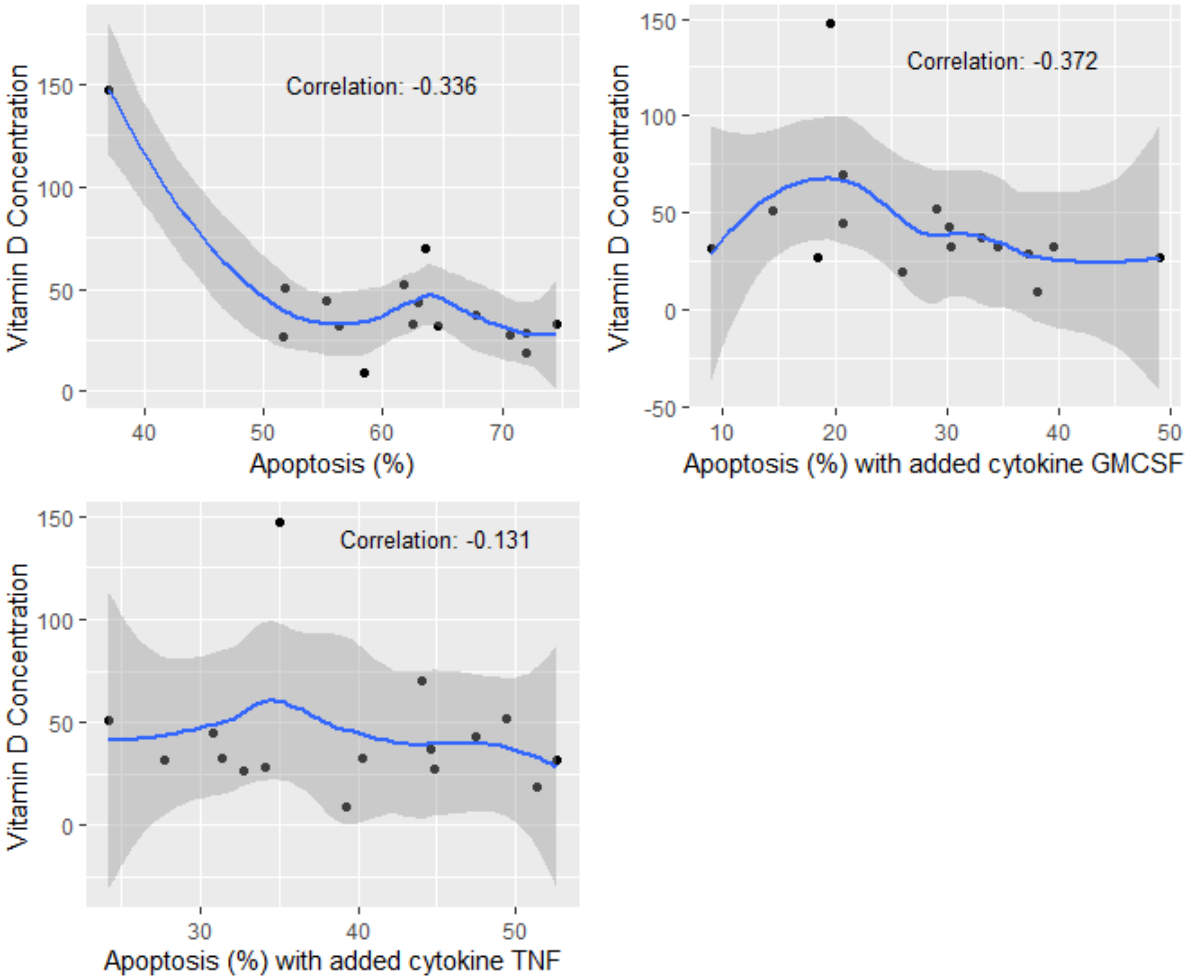
(Created using R_SATURN_Registration1, R_SATURN_VitaminDForm and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:10:10:26.)

Figure 18c – Panel of correlation plots between Vitamin D concentration and Neutrophil apoptosis %, at Week 24.



(Created using R_SATURN_Registration1, R_SATURN_VitaminDForm and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:10:48:42.)

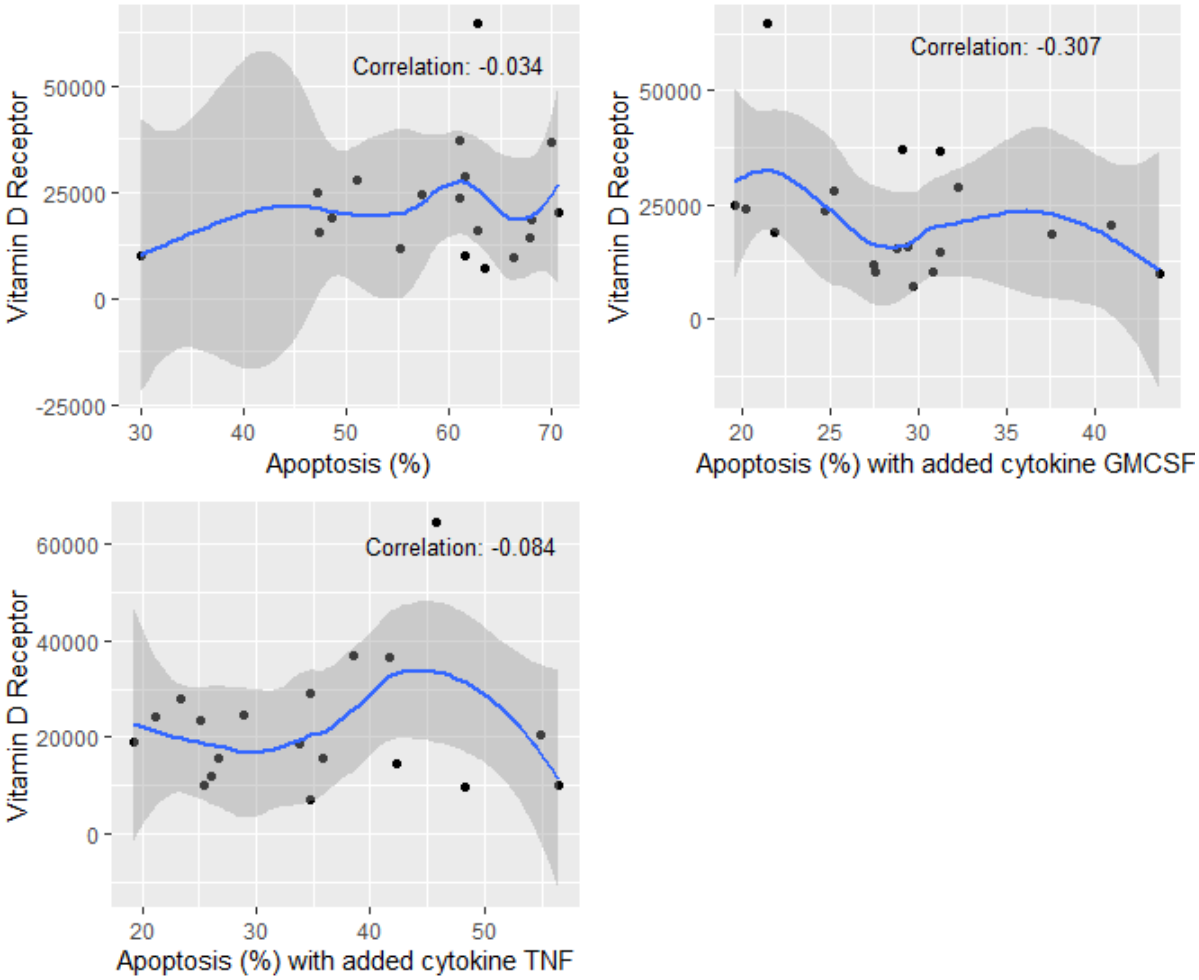
Figure 18d – Panel of correlation plots between Vitamin D concentration and Neutrophil apoptosis %, at Week 48.



(Created using R_SATURN_Registration1, R_SATURN_VitaminDForm and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:10:52:37.)

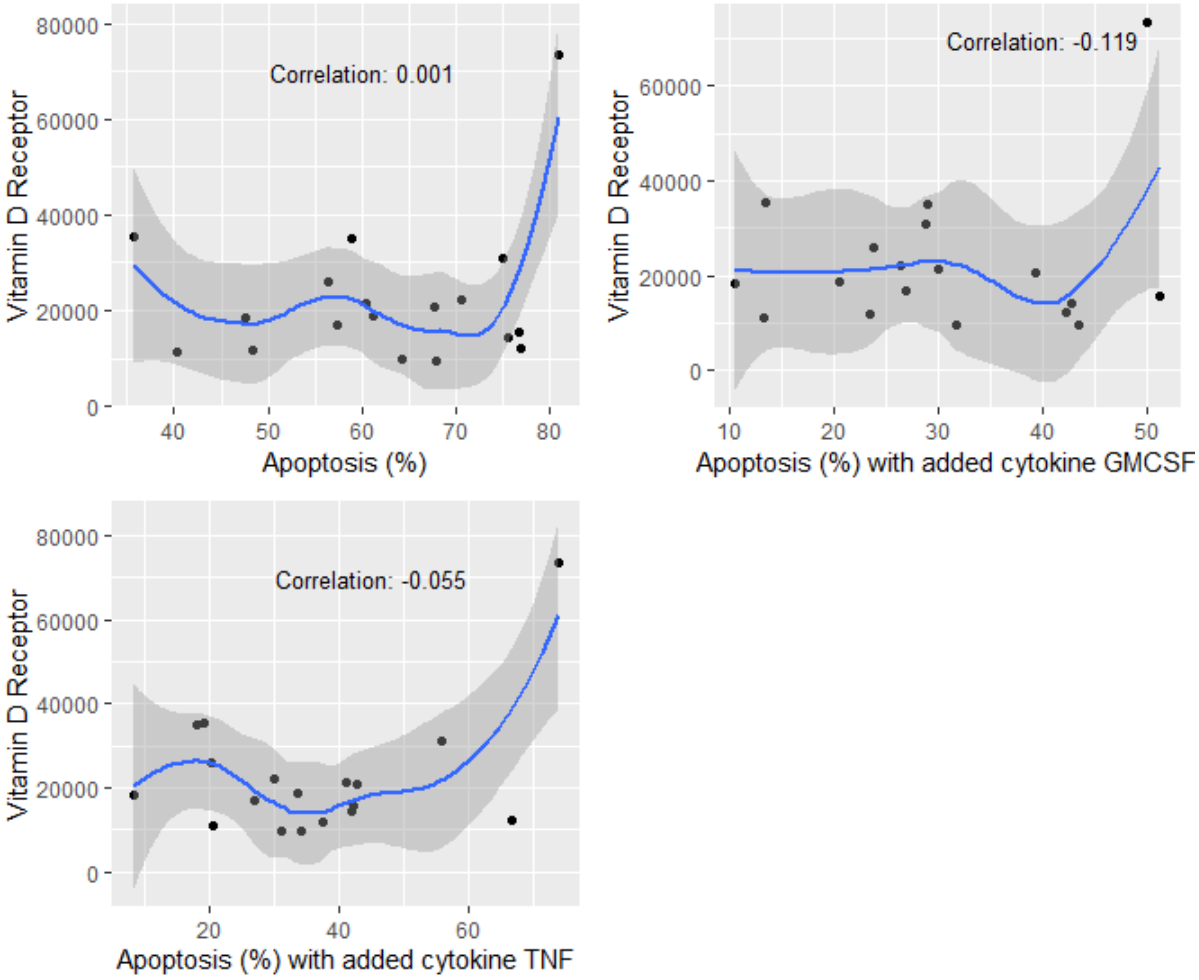
Figure 19a-19d, shows a panel of correlation plot between Neutrophil apoptosis % with and without cytokines and vitamin D receptor, at different time points.

Figure 19a – Panel of correlation plots between Vitamin D receptor and Neutrophil apoptosis %, at baseline.



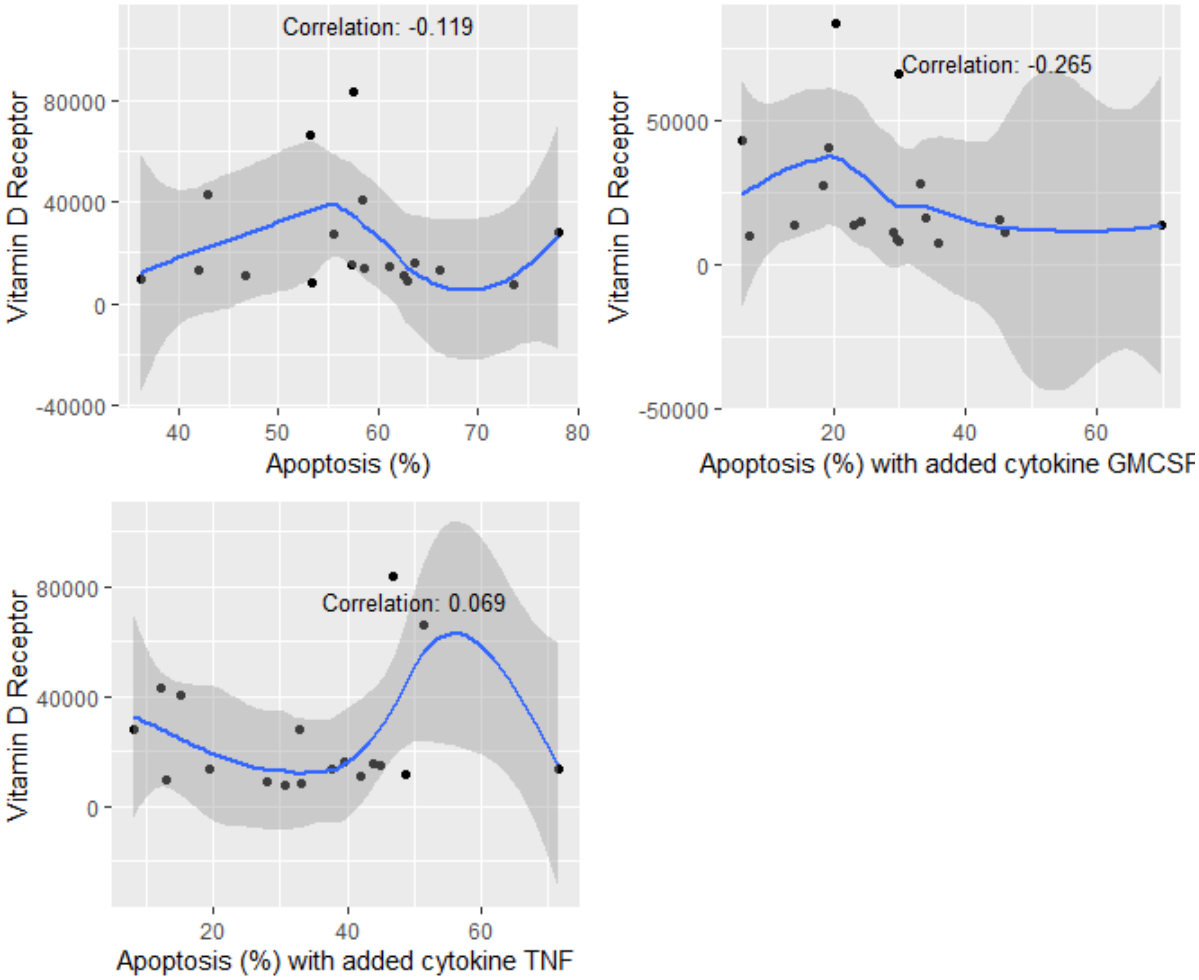
(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:11:17:43.)

Figure 19b – Panel of correlation plots between Vitamin D receptor and Neutrophil apoptosis %, at Week 12.



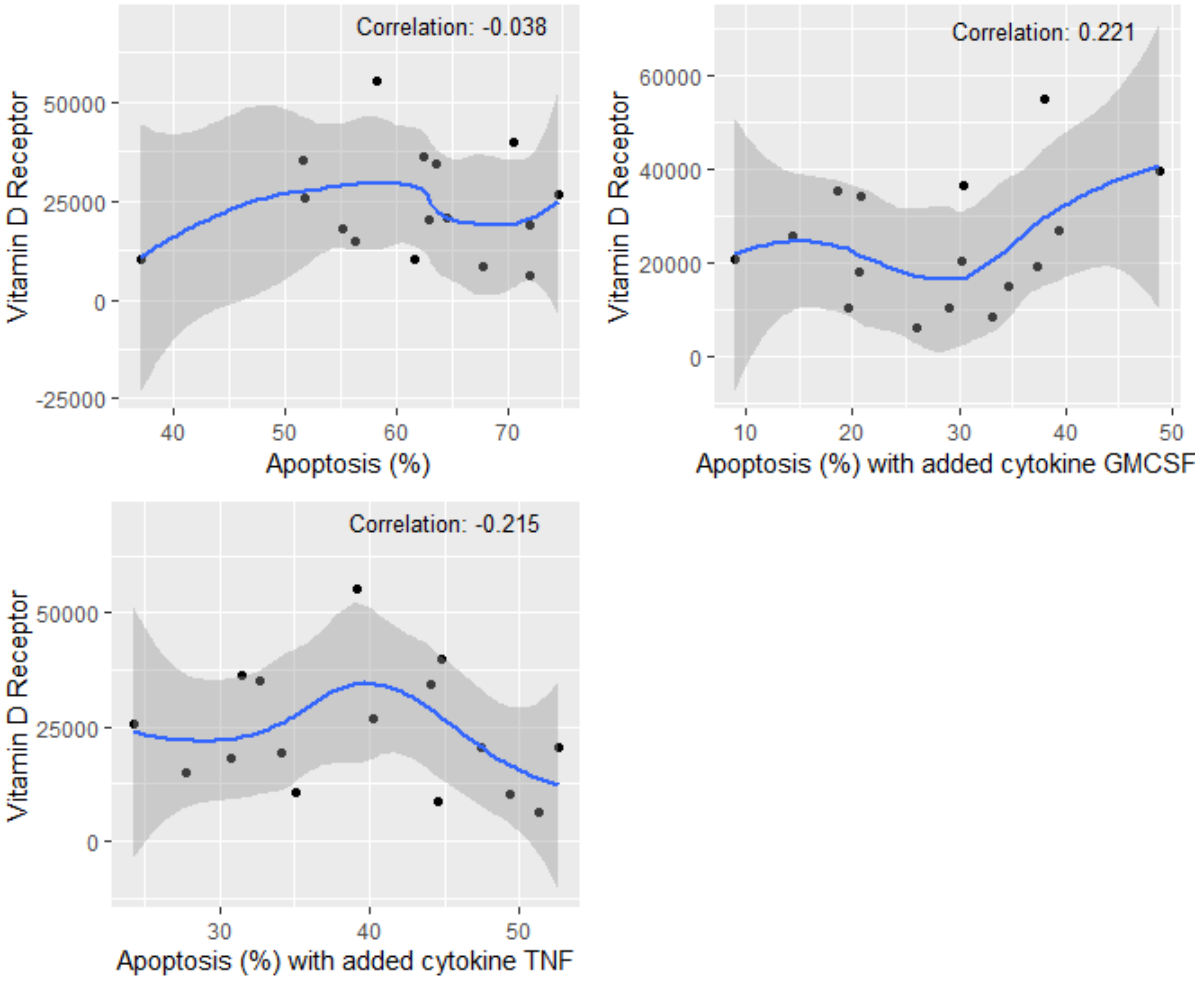
(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:11:21:02.)

Figure 19c – Panel of correlation plots between Vitamin D receptor and Neutrophil apoptosis %, at Week 24.



(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:11:24:40.)

Figure 19d – Panel of correlation plots between Vitamin D receptor and Neutrophil apoptosis %, at Week 48.



(Created using R_SATURN_Registration1, R_SATURN_SurfaceRec and R_SATURN_R_SATURN_Apoptosis found on Statistics Server by RG on 04NOV19:11:27:45.)

8.7 Analysis of Exploratory Outcomes

Clinical response

Tables 26-30 and Figures 20-24 give summary results for ACR20, PsARC, PASI 75, PASI 90 and NAPSI scores at each study visit.

When an improvement is calculated, if the patient at baseline has no disease or no pain etc., there is no ability for this patient to improve and therefore they will not be included in the calculation of scores in that area.

Note: Due to information provided post final analysis, the tables and figures for ACR20, PASI 75, PASI 90 and PsARC are updated from final analysis report version 1. These updates do not follow the SAP or methodology set out for the exploratory outcome clinical response variables. Initially the methodology states that these variables will be analysed via a longitudinal model, however on review of the definition of ACR20, PASI 75, PASI 90 and PsARC this is not appropriate as the result will be a binary variable based on improvement from baseline. Therefore, these variables will be summarised at each visit from baseline, presented via counts and percentages.

ACR20

ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: Patient global health assessment, physician global health assessment, HAQ score, VAS Pain score and Erythrocyte Sedimentation rate.

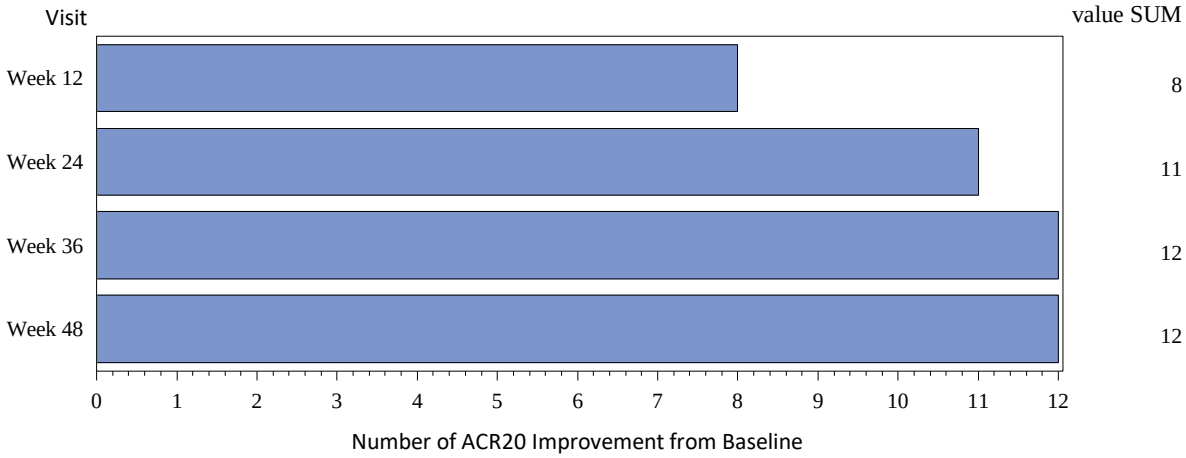
Table 26 is a summary of the number of patients showing a 20% improvement in ACR20 from baseline.

Table 26: Results for Exploratory Outcome – ACR20

Visit	Number of patients	Number of patients showing a 20% improvement in ACR20 from baseline.
Week 12	18	8 (44.4%)
Week 24	18	11 (61.1%)
Week 36	17	12 (70.6%)
Week 48	17	12 (70.6%)

(Created using R_SATURN_Registration1, r_saturn_clinicalass3, r_saturn_clinicalass4, r_saturn_qol_haqdi and r_saturn_bloods1 found on Statistics Server by RG on 06FEB20:15:52:18.)

Figure 20: The Number of Patients showing a 20% Improvement from Baseline in ACR20 Components



(Created using R_SATURN_Registration1, R_SATURN_Clinicalass3, R_SATURN_Clinicalass4, R_SATURN_QOL_Haqdi and R_SATURN_Bloods1 found on Statistics Server by RG on 06FEB20:15:54:09.)

PsARC

PsARC is composite measurement defined as an improvement in at least two of the four PsARC criteria (the number of tender joints, number of swollen joints, Patient global health assessment and physician global health assessment). One of these improvements has to be in the joint tenderness or swelling score, with no worsening in any of the four criteria.

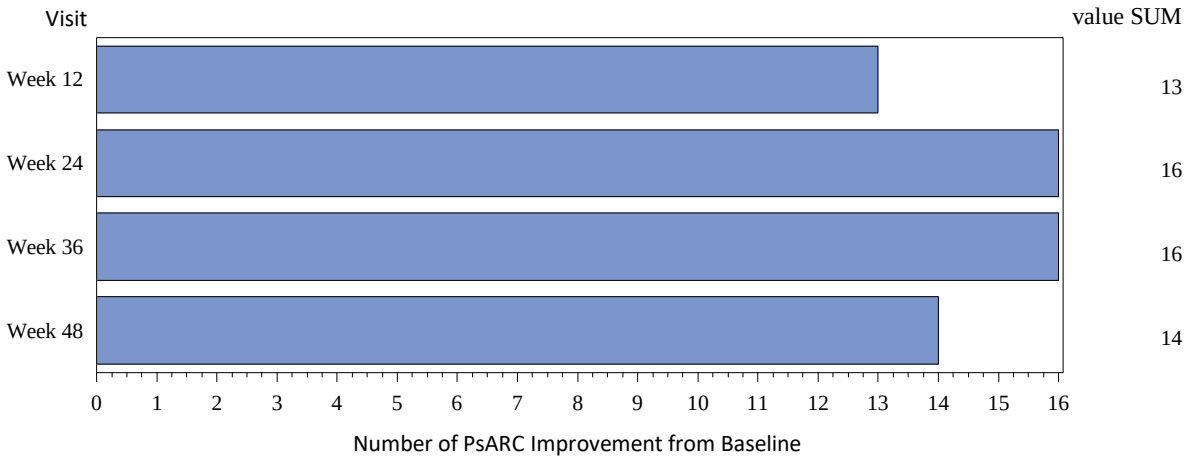
Table 27 is a summary of the number of patients showing an improvement in PsARC from baseline.

Table 27: Results for Exploratory Outcome – PsARC

Visit	Number of patients	Number of patients showing an improvement in PsARC from baseline.
Week 12	18	13 (72.2%)
Week 24	18	16 (88.9%)
Week 36	17	16 (94.1%)
Week 48	17	14 (82.4%)

(Created using R_SATURN_Registration1, R_SATURN_Clinicalass3 and R_SATURN_Clinicalass4 found on Statistics Server by RG on 06FEB20:15:56:22.)

Figure 21: The Number of Patients showing an Improvement from Baseline in PsARC Components



(Created using R_SATURN_Registration1, R_SATURN_Clinicalass3 and R_SATURN_Clinicalass4 found on Statistics Server by RG on 06FEB20:15:57:01.)

PASI 75

Psoriasis area and severity index (PASI) is a widely used tool for the measurement of severity of psoriasis. It combines the assessment of the severity of lesions and the are affected into a single score that ranges from 0 (no disease) to 72 (maximal disease).

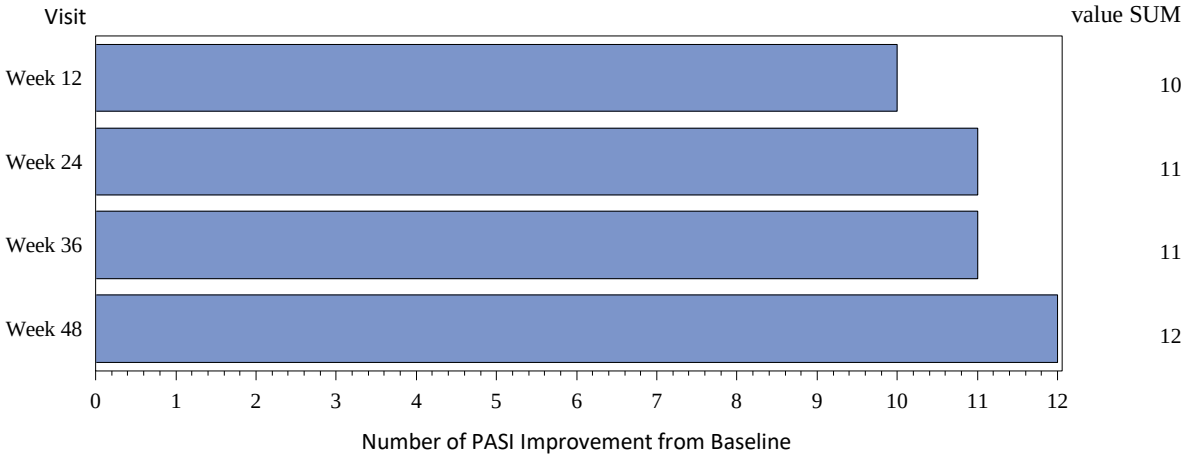
PASI 75 represents the number of patients who have achieved a 75% or more reduction in their PASI score from baseline.

Table 28: Results for Exploratory Outcome – PASI 75

Visit	Number of patients	Number of patients showing a 75% improvement in PASI from baseline.
Week 12	16	10 (62.5%)
Week 24	16	11 (68.8%)
Week 36	15	11 (73.3%)
Week 48	15	12 (80.0%)

(Created using R_SATURN_Registration1 and R_SATURN_Clinicalass2 found on Statistics Server by RG on 06FEB20:15:57:56.)

Figure 22: The Number of Patients showing a 75% Improvement from Baseline in PASI score



(Created using R_SATURN_Registration1 and R_SATURN_Clinicalass2 found on Statistics Server by RG on 06FEB20:15:58:39.)

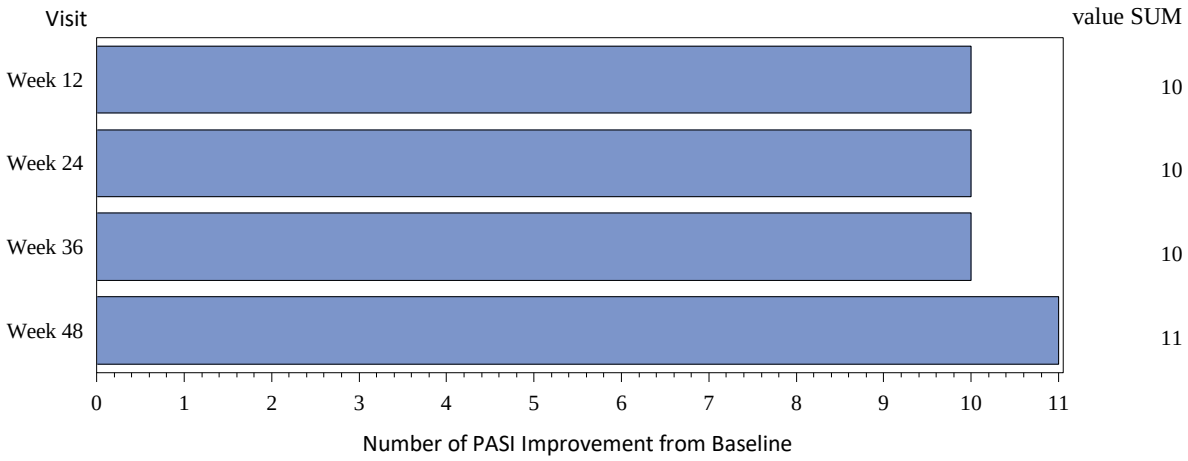
PASI 90

PASI 90 represents the number of patients who have achieved a 90% or more reduction in their PASI score from baseline.

Table 29: Results for Exploratory Outcome – PASI 90		
Visit	**Number of patients**	**Number of patients showing a 90% improvement in PASI from baseline.**
Week 12	16	10 (62.5%)
Week 24	16	10 (62.5%)
Week 36	15	10 (66.7%)
Week 48	15	11 (73.3%)

(Created using R_SATURN_Registration1 and R_SATURN_Clinicalass2 found on Statistics Server by RG on 06FEB20:16:01:07.)

Figure 23: The Number of Patients showing a 90% Improvement from Baseline in PASI Components



(Created using R_SATURN_Registration1 and R_SATURN_Clinicalass2 found on Statistics Server by RG on 06FEB20:16:01:47.)

NAPSI

Table 30: Results for Exploratory Outcome - NAPSI

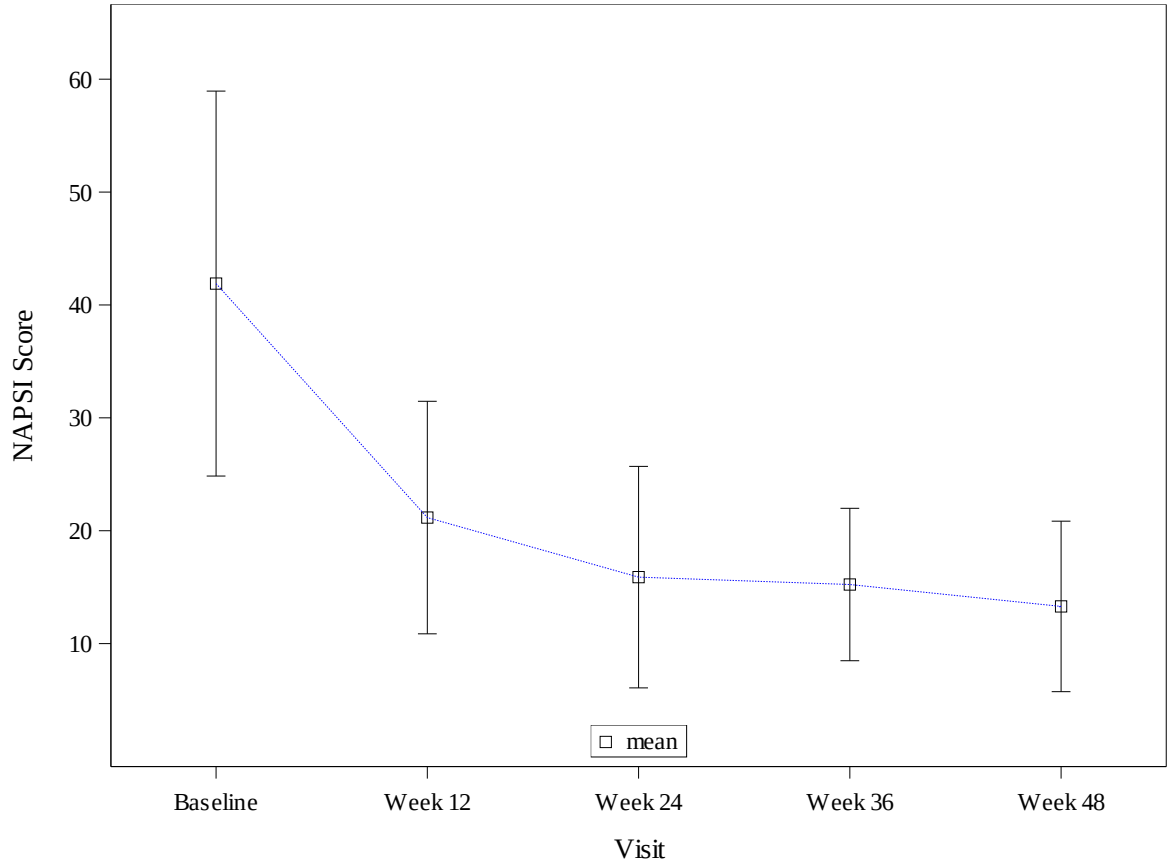
Table 30: Results for Exploratory Outcome - NAPSI				
Arm	**Longitudinal Model**	**Estimate (Standard Error)**	**95% Confidence Interval**	**LSE* (95% Confidence Interval)**
Secukinumab	Intercept	41.89 (5.18)	(31.01, 52.78)	-
	Visit (Baseline)	-	-	41.89 (31.55, 52.24)
	Visit (Week 12)	-21.52 (5.13)	(-31.77, -11.27)	20.38 (9.83, 30.92)
	Visit (Week 24)	-26.80 (5.13)	(-37.04, -16.55)	15.10 (4.55, 25.65)
	Visit (Week 36)	-26.72 (5.23)	(-37.15, -16.28)	15.18 (4.45, 25.91)
	Visit (Week 48)	-28.66 (5.23)	(-39.09, -18.22)	13.24 (2.50, 23.97)

*Least Squares Estimate

(Created using R_SATURN_Registration1 and R_SATURN_Clinicalass1 found on Statistics Server by RG on 29NOV19:10:28:13.)

Table 30, shows that compared to baseline there is a statistically significant difference at the 5% level in Weeks 12, 24, 36 and 48.

Figure 24: NAPSI Score for Secukinumab Patients over Time



Graph shows the raw mean and 95% confidence interval.
(Created using R_SATURN_Registration1 and R_SATURN_Clinicalass1 found on Statistics Server by RG on 11NOV19:13:37:59.)

Quality of Life

Tables 31-32 and Figures 25-28 give summary results of EQ5D and HAQ at each study visit.

Each individual component of the EQ5D is scored between 1 and 5. Summaries are presented using the component counts. Percentages and mean (95% confidence interval). A high score by component indicates worse health. Overall health is directly measured using a Visual Analogue Scale (VAS) score and summarised as mean (95% confidence interval). A high VAS score indicates a better health.

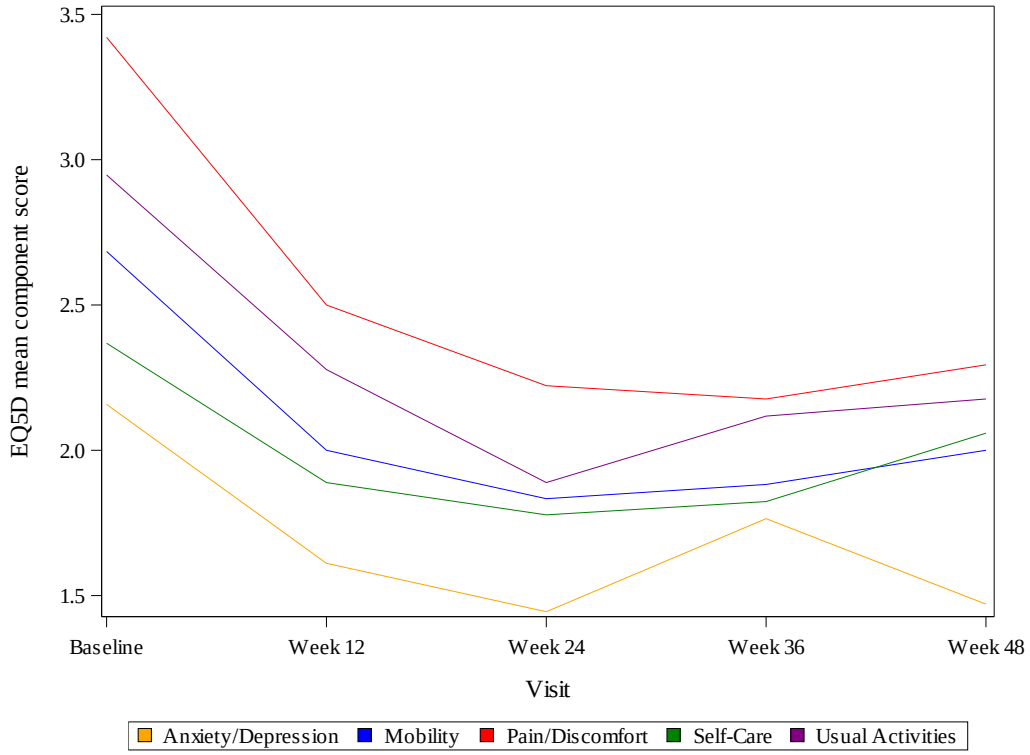
For reference the levels are graded as follows:
Level 1 – No Problem
Level 2 – Slight Problem
Level 3 – Moderate Problem
Level 4 – Severe Problem
Level 5 – Unable.

Table 31: Quality of Life EQ5D					
EQ5D QoL Component	**Baseline (N=19)**	**12 Weeks (N=19)**	**24 Weeks (N=19)**	**36 Weeks (N=19)**	**48 Weeks (N=19)**
Mobility					
Level 1, n (%)	3 (15.8)	7 (36.8)	8 (42.1)	9 (47.4)	8 (42.1)
Level 2, n (%)	5 (26.3)	5 (26.3)	6 (31.6)	2 (10.5)	3 (15.8)
Level 3, n (%)	7 (36.8)	5 (26.3)	3 (15.8)	5 (26.3)	4 (21.1)
Level 4, n (%)	3 (15.8)	1 (5.3)	1 (5.3)	1 (5.3)	2 (10.5)
Level 5, n (%)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	2.7 (2.2, 3.2)	2.0 (1.5, 2.5)	1.8 (1.4, 2.3)	1.9 (1.3, 2.4)	2.0 (1.4, 2.6)
Difficulties with Self-Care					
Level 1, n (%)	5 (26.3)	6 (31.6)	9 (47.4)	8 (42.1)	8 (42.1)
Level 2, n (%)	5 (26.3)	8 (42.1)	5 (26.3)	4 (21.1)	3 (15.8)
Level 3, n (%)	6 (31.6)	4 (21.1)	3 (15.8)	5 (26.3)	3 (15.8)
Level 4, n (%)	3 (15.8)	0 (0.0)	1 (5.3)	0 (0.0)	3 (15.8)
Level 5, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	2.4 (1.9, 2.9)	1.9 (1.5, 2.3)	1.8 (1.3, 2.2)	1.8 (1.4, 2.3)	2.1 (1.4, 2.7)
Difficulties with Usual Activities					
Level 1, n (%)	2 (10.5)	5 (26.3)	9 (47.4)	6 (31.6)	5 (26.3)
Level 2, n (%)	4 (21.1)	6 (31.6)	3 (15.8)	5 (26.3)	7 (36.8)
Level 3, n (%)	8 (42.1)	4 (21.1)	5 (26.3)	5 (26.3)	2 (10.5)
Level 4, n (%)	3 (15.8)	3 (15.8)	1 (5.3)	0 (0.0)	3 (15.8)
Level 5, n (%)	2 (10.5)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	2.9 (2.4, 3.5)	2.3 (1.7, 2.8)	1.9 (1.4, 2.4)	2.1 (1.5, 2.7)	2.2 (1.6, 2.7)
Pain/ Discomfort					
Level 1, n (%)	1 (5.3)	1 (5.3)	4 (21.1)	4 (21.1)	4 (21.1)
Level 2, n (%)	0 (0.0)	9 (47.4)	9 (47.4)	8 (42.1)	8 (42.1)
Level 3, n (%)	10 (52.6)	6 (31.6)	3 (15.8)	3 (15.8)	2 (10.5)
Level 4, n (%)	6 (31.6)	2 (10.5)	1 (5.3)	2 (10.5)	2 (10.5)
Level 5, n (%)	2 (10.5)	0 (0.0)	1 (5.3)	0 (0.0)	1 (5.3)

Table 31: Quality of Life EQ5D					
EQ5D QoL Component	**Baseline (N=19)**	**12 Weeks (N=19)**	**24 Weeks (N=19)**	**36 Weeks (N=19)**	**48 Weeks (N=19)**
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	3.4 (3.0, 3.9)	2.5 (2.1, 2.9)	2.2 (1.7, 2.7)	2.2 (1.7, 2.7)	2.3 (1.7, 2.9)
Anxiety/ Depression					
Level 1, n (%)	7 (36.8)	10 (52.6)	14 (73.7)	8 (42.1)	12 (63.2)
Level 2, n (%)	6 (31.6)	6 (31.6)	1 (5.3)	6 (31.6)	2 (10.5)
Level 3, n (%)	2 (10.5)	1 (5.3)	2 (10.5)	2 (10.5)	3 (15.8)
Level 4, n (%)	4 (21.1)	1 (5.3)	1 (5.3)	1 (5.3)	0 (0.0)
Level 5, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	2.2 (1.6, 2.7)	1.6 (1.2, 2.0)	1.4 (1.0, 1.9)	1.8 (1.3, 2.2)	1.5 (1.1, 1.9)
Overall Health score (VAS)					
Mean (95% CI)	51.3 (40.9, 61.7)	72.5 (62.0, 83.0)	73.4 (62.7, 84.1)	72.4 (60.8, 83.9)	71.1 (58.5, 83.7)

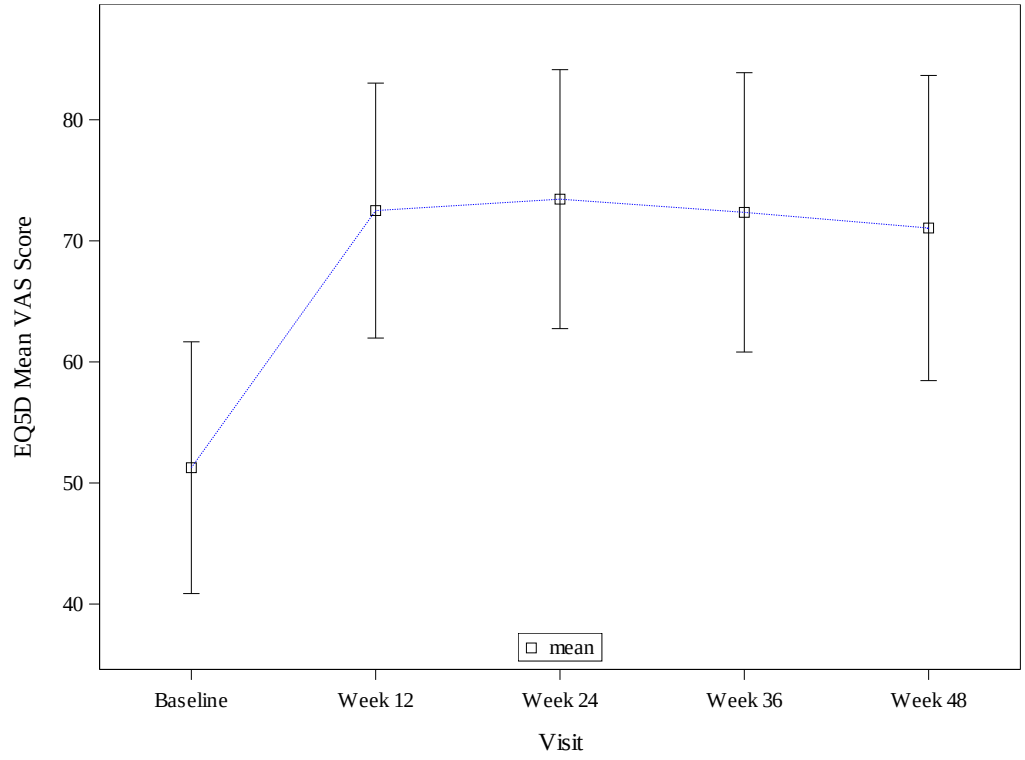
(Created using R_SATURN_Registration1 and R_SATURN_EQ5D found on Statistics Server by RG on 11NOV19:13:16:30.)

Figure 25: EQ5D mean scores for Secukinumab Patients Over Time by Components



(Created using R_SATURN_Registration1 and R_SATURN_EQ5D found on Statistics Server by RG on 11NOV19:15:01:47.)

Figure 26: EQ5D mean Overall Health (VAS) Score for Secukinumab Patients Over Time



(Created using R_SATURN_Registration1 and R_SATURN_EQ5D found on Statistics Server by RG on 11NOV19:13:57:37.)

The HAQ score is divided in 8 categories, with each category scored 0-3. Summaries of the score for each of these 8 categories are presented using the counts, percentages and mean (95% confidence interval). The overall HAQ score is presented by the mean (95% confidence interval). A high score indicates a worse health.

For reference the levels are graded as follows:
Level 0 – Without Any Difficulty
Level 1 – With Some Difficulty
Level 2 – With Much Difficulty
Level 3 – Unable

Table 32: Quality of Life HAQ

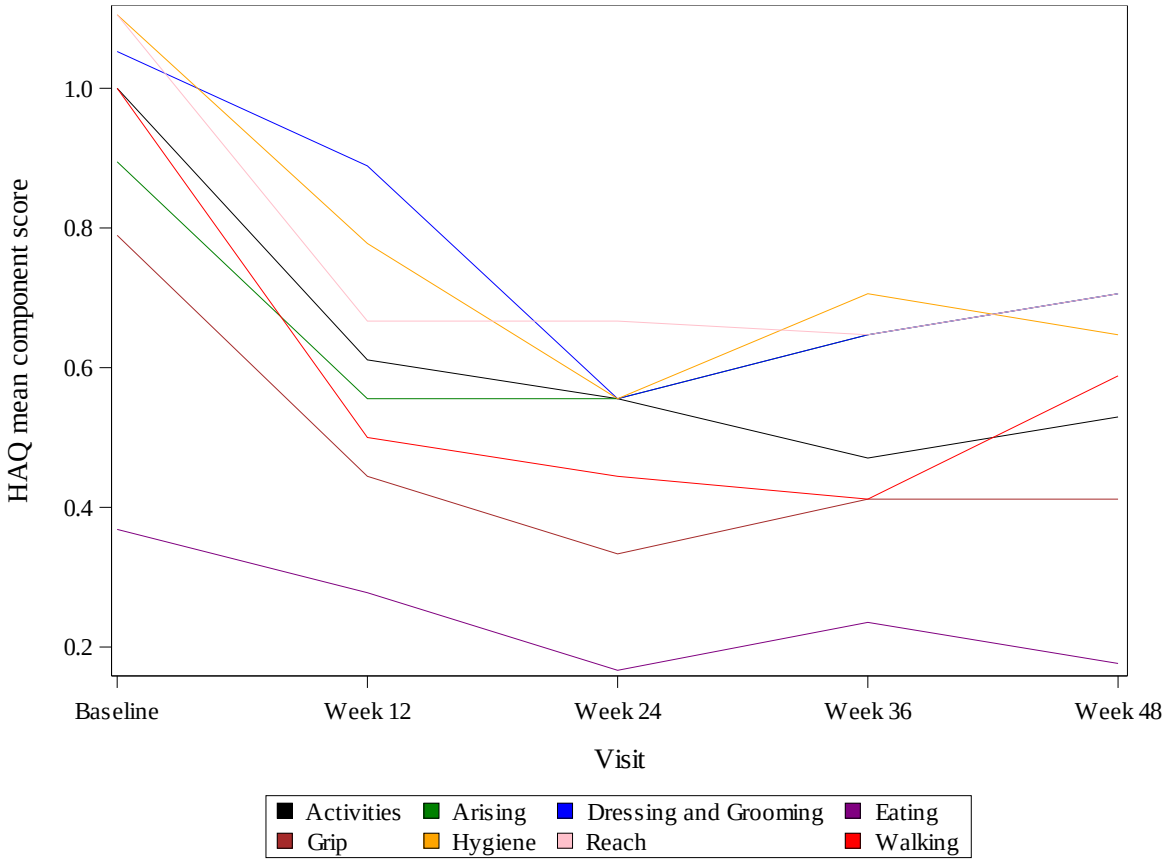
HAQ QoL Component	Baseline (N=19)	12 Weeks (N=19)	24 Weeks (N=19)	36 Weeks (N=19)	48 Weeks (N=19)
Dressing and Grooming					
Level 0, n (%)	4 (21.1)	4 (21.1)	10 (52.6)	8 (42.1)	7 (36.8)
Level 1, n (%)	10 (52.6)	12 (63.2)	6 (31.6)	7 (36.8)	8 (42.1)
Level 2, n (%)	5 (26.3)	2 (10.5)	2 (10.5)	2 (10.5)	2 (10.5)
Level 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	1.1 (0.7, 1.4)	0.9 (0.6, 1.2)	0.6 (0.2, 0.9)	0.6 (0.3, 1.0)	0.7 (0.4, 1.1)
Arising					
Level 0, n (%)	7 (36.8)	10 (52.6)	11 (57.9)	9 (47.4)	9 (47.4)
Level 1, n (%)	7 (36.8)	6 (31.6)	4 (21.1)	5 (26.3)	4 (21.1)
Level 2, n (%)	5 (26.3)	2 (10.5)	3 (15.8)	3 (15.8)	4 (21.1)
Level 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	0.9 (0.5, 1.3)	0.6 (0.2, 0.9)	0.6 (0.2, 0.9)	0.6 (0.2, 1.1)	0.7 (0.3, 1.1)
Eating					
Level 0, n (%)	12 (63.2)	13 (68.4)	15 (78.9)	13 (68.4)	14 (73.7)
Level 1, n (%)	7 (36.8)	5 (26.3)	3 (15.8)	4 (21.1)	3 (15.8)
Level 2, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Level 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)

Table 32: Quality of Life HAQ					
HAQ QoL Component	**Baseline (N=19)**	**12 Weeks (N=19)**	**24 Weeks (N=19)**	**36 Weeks (N=19)**	**48 Weeks (N=19)**
Mean (95% CI)	0.4 (0.1, 0.6)	0.3 (0.0, 0.5)	0.2 (0.0, 0.4)	0.2 (0.0, 0.5)	0.2 (0.0, 0.4)
Walking					
Level 0, n (%)	4 (21.1)	10 (52.6)	12 (63.2)	12 (63.2)	9 (47.4)
Level 1, n (%)	12 (63.2)	7 (36.8)	4 (21.1)	4 (21.1)	7 (36.8)
Level 2, n (%)	2 (10.5)	1 (5.3)	2 (10.5)	0 (0.0)	0 (0.0)
Level 3, n (%)	1 (5.3)	0 (0.0)	0 (0.0)	1 (5.3)	1 (5.3)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	1.0 (0.6, 1.4)	0.5 (0.2, 0.8)	0.4 (0.1, 0.8)	0.4 (0.0, 0.8)	0.6 (0.2, 1.0)
Hygiene					
Level 0, n (%)	4 (21.1)	7 (36.8)	10 (52.6)	8 (42.1)	8 (42.1)
Level 1, n (%)	10 (52.6)	8 (42.1)	6 (31.6)	6 (31.6)	7 (36.8)
Level 2, n (%)	4 (21.1)	3 (15.8)	2 (10.5)	3 (15.8)	2 (10.5)
Level 3, n (%)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	1.1 (0.7, 1.5)	0.8 (0.4, 1.1)	0.6 (0.2, 0.9)	0.7 (0.3, 1.1)	0.6 (0.3, 1.0)
Reach					
Level 0, n (%)	4 (21.1)	9 (47.4)	10 (52.6)	9 (47.4)	9 (47.4)
Level 1, n (%)	9 (47.4)	6 (31.6)	4 (21.1)	5 (26.3)	4 (21.1)
Level 2, n (%)	6 (31.6)	3 (15.8)	4 (21.1)	3 (15.8)	4 (21.1)
Level 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	1.1 (0.7, 1.5)	0.7 (0.3, 1.0)	0.7 (0.2, 1.1)	0.6 (0.2, 1.1)	0.7 (0.3, 1.1)
Grip					
Level 0, n (%)	7 (36.8)	11 (57.9)	13 (68.4)	11 (57.9)	11 (57.9)
Level 1, n (%)	9 (47.4)	6 (31.6)	4 (21.1)	5 (26.3)	5 (26.3)
Level 2, n (%)	3 (15.8)	1 (5.3)	1 (5.3)	1 (5.3)	1 (5.3)
Level 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	0.8 (0.4, 1.1)	0.4 (0.1, 0.8)	0.3 (0.0, 0.6)	0.4 (0.1, 0.7)	0.4 (0.1, 0.7)
Activities					

Table 32: Quality of Life HAQ					
HAQ QoL Component	**Baseline (N=19)**	**12 Weeks (N=19)**	**24 Weeks (N=19)**	**36 Weeks (N=19)**	**48 Weeks (N=19)**
Level 0, n (%)	5 (26.3)	8 (42.1)	10 (52.6)	10 (52.6)	10 (52.6)
Level 1, n (%)	9 (47.4)	9 (47.4)	6 (31.6)	6 (31.6)	5 (26.3)
Level 2, n (%)	5 (26.3)	1 (5.3)	2 (10.5)	1 (5.3)	2 (10.5)
Level 3, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	19 (100.0)	18 (94.7)	18 (94.7)	17 (89.5)	17 (89.5)
Mean (95% CI)	1.0 (0.6, 1.4)	0.6 (0.3, 0.9)	0.6 (0.2, 0.9)	0.5 (0.1, 0.8)	0.5 (0.2, 0.9)
Overall HAQ score					
Mean (95% CI)	7.3 (5.2, 9.4)	4.7 (2.8, 6.7)	3.8 (1.6, 6.1)	4.2 (1.9, 6.5)	4.5 (2.2, 6.7)

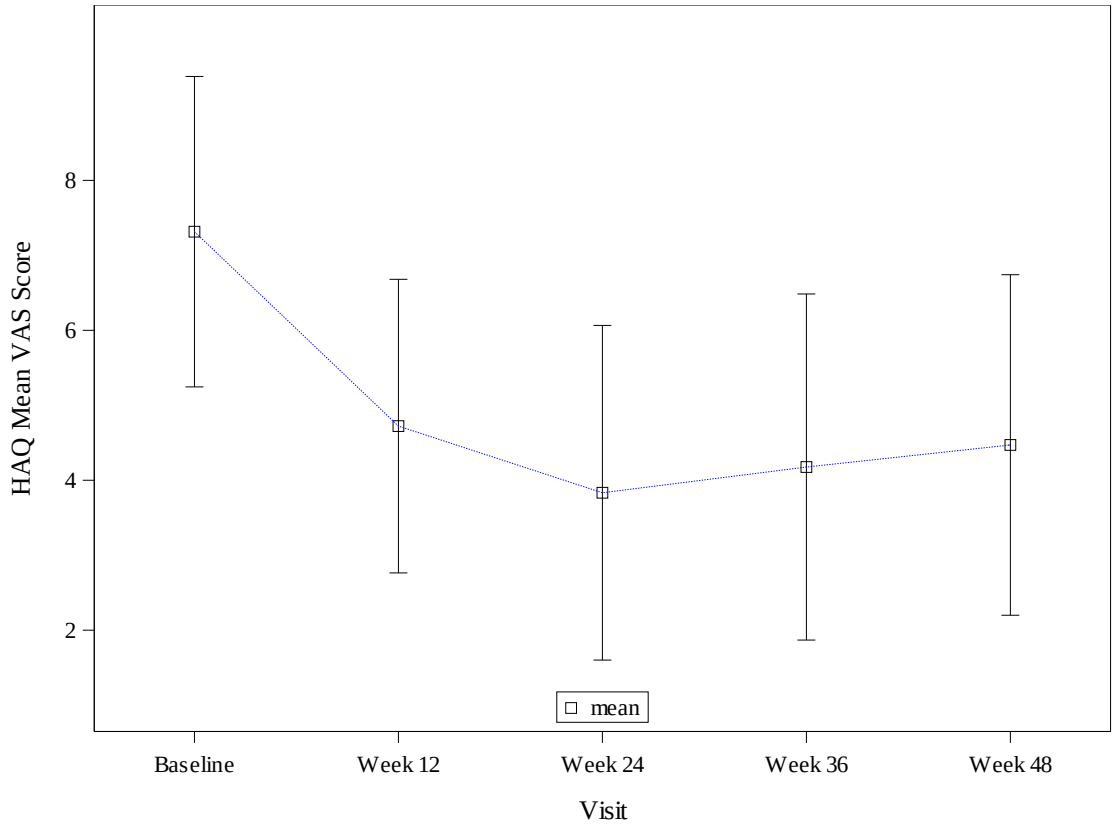
(Created using R_SATURN_Registration1 and R_SATURN_QOL_HAQDI found on Statistics Server by RG on 11NOV19:14:40:06.)

Figure 27: HAQ mean scores for Secukinumab Patients Over Time by Components



(Created using R_SATURN_Registration1 and R_SATURN_QOL_HAQDI found on Statistics Server by RG on 11NOV19:15:00:26.)

Figure 28: Overall Mean HAQ Score for Secukinumab Patients Over Time



(Created using R_SATURN_Registration1 and R_SATURN_QOL_HAQDI found on Statistics Server by RG on 11NOV19:15:05:14.)

9. SAFETY EVALUATION

Adverse events and Serious adverse events are coded in accordance with MedDRA version 19.0. The safety analysis set will be used from this point forward and consists of 19 patients. The patient allocated to the DMARD arm (prior to protocol v4.0) is not included in the safety set as they withdrew from the trial prior to receiving any treatment. Therefore, the following tables will only be reported by Secukinumab.

Table 33, provides a summary of the number of patients withdrawing because of toxicities.

Table 33: N (%) Patients Withdrawing due to Toxicity or SAE

NOTE: There were no patients who withdrew from treatment due to either a toxicity (grade 3+) or SAE, therefore this table has not been produced.

Table 34, shows the range of AE severity across the treatment Secukinumab, of all the reported adverse events. In total 19 patients have recorded 18 adverse events.

Table 34: Overview of Adverse Events by Severity

AE Severity Grade	Secukinumab n (%)
1	1 (5.6)
2	17 (94.4)
3	0 (0.0)
4	0 (0.0)
Total	18 (100.0)

(Created using R_SATURN_Registration1 and SNP_pv_ae found on Statistics Server by RG on 11NOV19:16:09:24.)

The following table shows the range of SAE severity across treatment Secukinumab, of all the reported serious adverse events. In total 19 patients have recorded 0 serious adverse events.

Table 35: Overview of Serious Adverse Events by Severity

NOTE: There has been no serious adverse events, therefore no table has been produced.

Table 36, shows a listing of patients experiencing at least one grade 3+ Adverse Event by the System Organ Class and Preferred term.

Table 36: Patients Experiencing at least one grade 3+ Adverse Event

NOTE: There are no grade 3+ adverse events reported, therefore this table is not applicable.

Table 37, shows a listing of patients experiencing at least one Serious Adverse Event by the System Organ Class and Preferred term.

Table 37: Patients experiencing at least one Serious Adverse Event

NOTE: There are no serious adverse events reported, therefore this table is no applicable.

10. DISCUSSION

Pivotal clinical trials have clearly shown that inhibition of IL-17 is effective in the management of PsA and PsO and has led to the licencing of two agents approved for use in these conditions. In this trial, we have observed high efficacy of the IL-17 inhibitor, secukinumab, not only for skin and joint, but also nails and entheses and patient-reported outcomes (PROMS). In addition, we did not find any significant adverse events, reinforcing the well-established reported safety profile.

Whilst the safety profile from reported clinical trials of IL-17 inhibitors are favourable, suggesting good tolerance with minimal if any clinical immunodeficiency, the interaction between IL-17, IL-17 inhibition and neutrophils, which are recently being considered to be key players in the immune system, have been poorly understood.

Conflicting reports suggest that, on the one hand, neutrophils may have the potential to amplify the inflammatory response in PsA by producing IL-17A, with identification of IL-17A-positive neutrophils both in psoriatic skin and the synovium of patients with PsA. However, other laboratories, unable to replicate these findings, have concluded that neutrophils can neither produce IL-17A protein or mRNA or protein, even after strong stimulation with relevant cytokines. There has therefore been a pressing need to investigate this further, both in vitro and in vivo – in patients on IL-17 inhibition – and correlate findings with clinical phenotype and response.

In this study, we confirmed that human neutrophils, from either our cohorts of healthy controls or patients with psoriatic arthritis could express IL-17, confirming recent published reports. In addition, we found that IL-17 could neither activate or prime control healthy neutrophils, using the range of assays that we used.

In psoriatic arthritis patients at baseline, there were no significant differences, compared to our age- and sex-matched healthy cohort in the ability of isolated neutrophils to generate ROS (after stimulation with a receptor-dependent and -independent agonist), undergo apoptosis (in the absence or presence of anti-apoptotic cytokines) or phagocytosis of serum-opsonised *Staphylococcus aureus*. There was a slightly decreased ability of neutrophils from psoriatic arthritis patients at baseline to undergo chemotaxis towards IL-8, compared to healthy controls, but this did not reach statistical significance.

Levels of expression of the surface expression of CD11b and CD18 both increased, while surface levels of CD16 decreased in psoriatic arthritis patients during therapy, compared to healthy controls. This would indicate that circulating neutrophil function is activated during treatment, even though disease activity improves. Our transcriptome analyses (to be included in a manuscript) confirm complex changes in the activation status of neutrophils pre- and post-therapy, with some metabolic pathways (such as cell signalling, chemokine-mediated cell signalling, chemotaxis as being **down-regulated** during therapy. However, several pathways associated with translation, mRNA catabolism, translation initiation were **up-regulated**.

These combined data indicate that during therapy, complex regulation of circulating neutrophil function occurs, with metabolic pathways increased (including receptor expression changes) and others decreased (receptor: signalling pathways). It is also a possibility that if local production of IL-8 is decreased via IL-17 inhibition, then fewer neutrophils will leave the circulation: hence there will be greater numbers of activated neutrophils in the circulation.

Finally, as a preliminary and exploratory arm of the study, we investigated the potential role of Vitamin D status in the interaction of neutrophils and IL-17 and did not find any significant interaction in that area, although the patient numbers were small. Initial results from this small observational study have highlighted a significant association between VitDdef and reduced initial response to secukinumab in PsA patients. This might reflect upregulation of IL-17 production in VitD deficient states. This requires testing in a larger study cohort. The potential impact of this work is to inform whether optimising vitamin D status prior to IL-17 inhibition will lead to better treatment response.

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End of Study Clinical Trial Report Approval

This confirms approval of the End of Study Clinical Trial Report for SATURN trial

Trial Co-ordinator

Name: Diane Carlton

Signature: .....

Date: 18/FEB/2020

Trial Statistician

Name: Rebecca Griffin

Signature: .....

Date: 18/FEB/2020

Chief Investigator

Name: Professor Robert J Moots

Signature: .....

Date: 24/FEB/2020