1. TITLE PAGE

CONFIDENTIAL

ABBREVIATED CLINICAL STUDY REPORT

Clinical Study Report Code: M-14745-44

Name of the investigational medicinal product: Not applicable
Indication studied: Moderate-to-severe chronic plaque psoriasis
Phase of the study: IV

"A PHASE IV INTERVENTIONAL STUDY TO ASSESS THE DISEASE-MODIFYING EFFECT OF LONG-TERM TREATMENT WITH TILDRAKIZUMAB IN ADULT PATIENTS WITH MODERATE-TO-SEVERE PLAQUE PSORIASIS"

(Protocol No. M-14745-44; Eudract No. 2019-003218-15)

Statistical Report No. (if applicable): Not applicable
Pharmacokinetics Report No. (if applicable): Not applicable
Date of initiation of the study: 29 January 2020
Date of early study termination (if applicable): 31 July 2020
Date of completion of the study: Not applicable
Date of completion of the Report: 15 January 2021

Company / Sponsor:
Almirall S.A.
Ronda General Mitre, 151
08022 Barcelona, Spain

Co-ordinating Investigator:
Prof. Jacek Szepietowski
Uniwersytecki Szpital Kliniczny im. Jana Mikulicza-Radeckiego we Wrocławiu
ul. Borowska 213,
50-556 Wroclaw, Poland
Phone: +48 71 327 09 41

Director Global Clinical Operations
Cristina Díaz Gallo
E-mail: Cristina.Diaz@almirall.com

The study was performed in accordance with Good Clinical Practices (GCP) including the archiving of essential documents

2. SYNOPSIS

Name of Sponsor / Company: Almirall, S.A. **Name of Finished Product:** N.A. **Name of Active Ingredients:** N.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of Study: A PHASE IV INTERVENTIONAL STUDY TO ASSESS THE DISEASE-MODIFYING EFFECT OF LONG-TERM TREATMENT WITH TILDRAKIZUMAB IN ADULT PATIENTS WITH MODERATE-TO-SEVERE PLAQUE PSORIASIS

Investigators:
This study was conducted by 3 investigators in Poland (see Appendix 16.1.4).

1) Prof. Jacek Szepietowski, 2) Dr. Jolanta Weglowska, 3) Prof. Anna Wozniacka

National co-ordinating investigator: Prof. Jacek Szepietowski, Uniwersytecki Szpital Kliniczny im. Jana Mikulicza-Radeckiego we Wrocławiu, Wroclaw, Poland
Co-ordinating Investigators: Dr. Jolanta Weglowska, dermMedica Sp. z o.o, Wroclaw, Poland; Prof. Anna Wozniacka, Uniwersytecki Szpital Kliniczny im.WAM - Centralny Szpital Weteranow, Łódź, Poland.

Study centres:
This study was conducted in a total of 2 sites (see Appendix 16.1.4).

1) Uniwersytecki Szpital Kliniczny im. Jana Mikulicza-Radeckiego we Wrocławiu, Wroclaw, Poland;
2) Uniwersytecki Szpital Kliniczny im.WAM - Centralny Szpital Weteranow, Łódź, Poland.

Publication (reference):
None

Studied period (years): Date study initiated (first screening): 29 January 2020 Date study finalised (last subject last visit): 28 August 2020	**Phase of development:** IV

Objectives:

Primary objective

To describe blood and skin inflammatory biomarkers and its correlation with psoriasis disease severity over time after having discontinued long-term treatment with tildrakizumab.

Secondary objectives

- To assess time to disease relapse in the overall and in the different tildrakizumab responder populations
- To assess changes in disease status (Psoriasis Area and Severity Index [PASI], Body surface area [BSA], Physician´s Global Assessment [PGA], nail PGA [nPGA], and scalp PGA [scPGA]) from baseline and until the End of Study (EoS)
- To assess changes in Patient Reported Outcomes (PROs) from baseline and until the EoS.

Name of Sponsor / Company: Almirall, S.A. **Name of Finished Product:** N.A. **Name of Active Ingredients:** N.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Methodology:

This was a multicentre, interventional, prospective, phase IV clinical study. The main aim was to evaluate the psoriasis disease control over time in patients who have received tildrakizumab for at least the last 5 years and have discontinued it and to describe blood and skin inflammatory biomarkers and its correlation with disease relapse. Overall, approximately 47 subjects from 3 centres in Poland were expected to be included. After a 6-month inclusion period, up to 9 visits every 12 weeks were scheduled. Subjects were to remain in the study for up to 96 weeks or until they initiate any systemic therapy for psoriasis (including phototherapy), whichever occured first.

The study was prematurely terminated by the Sponsor on 31 July 2020 due to the inability to recruit enough patients within the time frame established . A total of 9 of the initially planned 47 subjects were included in the study. As per the study design, only adult subjects who have completed the long-term extension of the reSURFACE 2 study in Poland were potentially eligible to be included in the present study. Thus, the subjects' pool was limited and irreplaceable.

All participating sites were promptly notified to discontinue ongoing subjects.

Number of subjects (planned and analysed):

	Total
Planned:	47
Screened:	9
Completed the study:	0
Full Analysis Set	9
Per-Protocol Set	5

Diagnosis and main criteria for inclusion:

Please see Section 9.3.

Test product, dose and mode of administration, batch number, expiry date:

Not applicable. Subjects did not receive any study medication during the study.

Duration of treatment:

Not applicable.

Reference therapy, dose and mode of administration, batch number, expiry date:

Not applicable.

Name of Sponsor / Company: Almirall, S.A **Name of Finished Product:** N.A. **Name of Active Ingredients:** N.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Criteria for evaluation:

Primary Variables:

- Blood and skin inflammatory biomarkers (YES [presence of inflammatory biomarkers]/NO [no presence of inflammatory biomarkers]) at each applicable visit

Skin biopsies were optional. None of the included patients granted permission for skin biopsies.

- Proportion of patients with psoriasis relapse during the 96-week follow-up period (YES [relapse]/ NO [disease control]), where relapse is defined using the following thresholds:

  - PASI >3* (in patients who had a PASI ≤3 at baseline)
  - PASI >5* (in patients who had a PASI ≤5 at baseline)
  - Dermatology Quality of Life Index **(**DLQI) >5* (in patients who had a DLQI ≤5 at baseline)
  - Initiation of any topical drug/medication for psoriasis†^
  - Initiation of any systemic therapy for psoriasis (biologic or non-biologic)†

*Only to be considered at first occurrence

†To be considered at every occurrence

^Only apply to topical drugs/medications (not soaps, shampoos, emollients, keratolytics, etc. will be included in this group)

Secondary Variables:

- Time to relapse during the 96-week follow-up period, defining relapse as the above mentioned categories

- Absolute PASI score and change from baseline in the absolute PASI score over time, and at EoS visit

- Absolute BSA score and change from baseline in the absolute BSA score over time, from baseline to EoS visit

- Absolute DLQI and DLQI-R scores and change from baseline in the absolute DLQI and DLQI-R scores over time, from baseline to EoS visit

- Absolute PGA, nPGA and scPGA scores and change in the absolute PGA, nail PGA and scalp PGA scores over time, from baseline to EoS visit

- Absolute pain- and pruritus-Numeric Rating Scale (NRS) scores and change from baseline in the absolute pain- and pruritus-NRS scores over time, from baseline to EoS visit

- Safety outcomes will include adverse events, physical examination, vital signs, and clinical laboratory assessments (haematology and biochemistry)

Statistical methods:

Analysis Populations

Due to the early termination of the study, there was only one statistical analysis population:

The Full Analysis Set (FAS) was defined as all patients who attended baseline visit and received a patient number.

A Per Protocol population (PP) was also defined in the protocol, although due to the limited number of subjects included none of the statistical evaluations were repeated for a PP.

Statistical Methods

The statistical approach for the analysis of primary and secondary variables is described below. Further specification of the analyses can be found in Appendix 16.1.9.

Due to the early termination of the study, the analyses defined in the Statistical Analysis Plan (SAP) have been changed and adapted from the clinical study protocol (CSP):

- Primary and some secondary objectives (relapse during the 96-week follow-up period and time to relapse) were impossible to asses because there were no data collected.
- Other objectives as changes from baseline or shift tables for laboratory values, vital signs or physical examination were removed from the analysis because there were not enough data collected in the study.

SUMMARY – CONCLUSIONS

Efficacy Results:

Due to the early study termination, only 9 subjects were included, and none of them finalized the 96 weeks of follow up. Therefore, the evolution of psoriasis over time once tildrakizumab is stopped could not be analysed. As a result, there are no efficacy conclusions.

Safety Results:

A total of 7 AEs were reported in 4 (44.4%) subjects, of which one was of moderate severity (exacerbation of psoriasis) and 6 were of mild severity (radiculitis [n=1], hair loss [n=1], uterine dilation and curettage [n=1], dyslipidemia [n=1] and exacerbation of psoriasis [n=2]). None of the AEs was serious, fatal or led to discontinuation of the study.

CONCLUSIONS:

This was a phase IV study that aimed to evaluate the disease-modifying effect of long-term treatment with tildrakizumab in adult patients with moderate-to-severe plaque psoriasis. The study was terminated prematurely with 9 subjects included at that time. The reason for study termination was due to the inability to recruit enough patients within the time frame established.

Due to the early study termination and limited data, the evolution of psoriasis disease severity over time after having discontinued long-term treatment with tildrakizumab could not be analysed; therefore, this study could not report any conclusion.

DATE OF REPORT:
15 January 2021

3. TABLE OF CONTENTS

CONTENT **PAGE**

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
BMI	Body Mass Index (weight in kg/height in m^2)
BSA	Body surface area
CI	Confidence Interval
CRO	Clinical Research Organization
CSP	Clinical Study Protocol
DLQI	Dermatology life quality index
DLQI-R	Dermatology life quality index – modified scoring
eCRF	electronic Case Report Form
EoS	End of Study
FAS	Full Analysis set
GCP	Good Clinical Practice
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
nPGA	nail Physician´s Global Assessment
NRS	Numeric Rating Scale
PASI	Psoriasis Area and Severity Index
PGA	Physician´s Global Assessment
PP	Per Protocol
PRO	Patient Reported Outcome
Q1	First quartiles
Q3	Third quartiles
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
scPGA	scalp Physician´s Global Assessment
TFS	Trial Form Support

5. ETHICS

5.1. INDEPENDENT ETHICS COMMITTEE (IEC) or INSTITUTIONAL REVIEW BOARD (IRB)

The final study protocol was reviewed and approved by an Independent Ethics Committee (IEC) for each centre prior to inclusion of subjects.

The name(s) and affiliation(s) of the IEC(s) are listed in Appendix 16.1.3.

5.2. ETHICAL CONDUCT OF THE STUDY

The study was conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

5.3. SUBJECT INFORMATION AND CONSENT

All subjects received written and verbal information regarding the study. The given information emphasised that participation in the study was voluntary and that the subject could withdraw from the study at any time and for any reason. All subjects were given the opportunity to ask questions about the study and were given sufficient time to decide whether to participate in the study.

Before any study-related procedures, the informed consent form (ICF) was signed and personally dated by the subject and by the person who conducted the informed consent discussion.

The consent included information that data was recorded, collected, processed and could be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data did not identify any persons taking part in the study.

An example of the subject information, including the informed consent form, is included in Appendix 16.1.3.

5.4. SUBJECT DATA PROTECTION

Subjects were identified in the Case Report Form (CRF) by the assigned study number. Study subjects were informed by the Investigator that complete confidentiality would be kept concerning their identity. A signed written Informed Consent confirmed the explicit acceptance by the individual that data from the study would be available to the Investigator and his staff, the representatives of the Sponsor and, if required, the IEC/IRB and regulatory authorities. However, all data contained in the subjects' medical records and any trial related document was considered confidential.

All data derived from this study were processed and treated in strict accordance to the Data Privacy Directive of the European Union.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1. SPONSOR

ALMIRALL, S.A.
Research Centre
Laureà Miró, 408-410
08980 Sant Feliu de Llobregat
Barcelona (Spain)
Phone: +34 93 291 30 00
Fax: +34 93 291 35 33

Director Global Clinical Operations:	Cristina Díaz
Clinical Operations Lead (Medical designee):	Èric Massana Montejo
Medical Safety Specialist:	Bernabé Proto Marco
Head of Global Statistics:	Meritxell Falqués
Statistician:	Guillem Carretero
Clinical Data Lead:	Mariya Ganeva

6.2. INVESTIGATOR(S)

This study was conducted by 3 investigators at 3 sites in Poland.
The names, affiliations, and CVs of these investigators are in Appendix 16.1.4.

The co-ordinating investigators are indicated below.

National Coordinating Investigator — Prof. Jacek Szepietowski

Uniwersytecki Szpital Kliniczny im. Jana Mikulicza-Radeckiego we Wrocławiu
ul. Borowska 213, 50-556 Wroclaw, Poland
Telephone: +48 71 327 09 41
E-mail: jacek.szepietowski@umed.wroc.pl

Co-ordinating Investigator — Dr. Jolanta Weglowska

dermMedica Sp. z o.o.
ul. Zakrzowska 19 a
51-318 Wroclaw, Poland
Telephone:+48 71 327 03 14
E-mail: jolaweglowska@tlen.pl

Co-ordinating Investigator — Prof. Anna Wozniacka

Uniwersytecki Szpital Kliniczny im.WAM - Centralny Szpital Weteranow
Pl. Hallera 1
94-647 Łódź, Poland
Telephone:+48 42 686 79 81
E-mail: wozniacka@bmp.net.pl

6.3. MONITORING CRO(s)

Trial Form Support
Medicon Village, Scheelevägen 2,
Lund, Sweden
Telephone:+46 462 801 800 (switchboard)
Fax: +46 462 801 801

Project Manager — Juliana Freiin von Berlepsch

6.4. OTHERS

The following companies participated in the study activities as indicated below (central laboratory, central ECG, clinical trial supply management, data management, statistics, pharmacy, bioanalysis laboratory, etc).

Role	Company / Address
Drug Safety Officer	**Trial Form Support Sp. z o.o.** ul. Grójecka 208 02-390 Warsaw, Poland E-mail: Katarzyna.Pustelnik@tfscro.com
Main contact:	Katarzyna Pustelnik
Data Management	**Trial Form Support S.L.** Consell de Cent 334, 08009 Barcelona, Spain Email: Valeria.Poli@tfscro.com
Main contact:	Valeria Poli
Statistical Analysis	**Trial Form Support S.L.** Consell de Cent 334, 08009 Barcelona, Spain Email: ramon.dosantos@tfsro.com
Main contact:	Ramon Dosantos Climent
Clinical Study Report Writing	**Trial Form Support S.L.** Consell de Cent 334, 08009 Barcelona, Spain Email: Cristina.Ceballos@tfscro.com
Main contact:	Cristina Ceballos

7. INTRODUCTION

7.1. BACKGROUND INFORMATION

Psoriasis is a chronic relapsing/remitting, inflammatory, immune-mediated systemic skin disease. Plaque psoriasis (psoriasis vulgaris) is the most common type of psoriasis, characterized by sharply demarcated erythematous and scaly lesions/plaques with a silvery appearance [1,2].

Clinical experience shows that people with psoriasis differ widely with individual disease expressions and personal perceptions of disease burden and treatment success. Treatments used to control psoriasis also differ with regard to efficacy, degree of toxicity, treatment effort, and cost. Therefore, patient-oriented care demands for physicians to align the choice of psoriasis medication with preferences and treatment goals of each patient [3,4]. Thus, treatment options for people with psoriasis depend on disease severity, comorbidities and patient choice. Usually, moderate-to-severe psoriasis is treated with systemic drugs, either non-biologic (e.g. immunosuppressive drugs as methotrexate and cyclosporine, retinoids, inhibitors of phosphodiesterase-4 and fumarates) or biologic agents (e.g. tumour necrosis factor-alpha inhibitors, IL-17 inhibitors, IL-17 receptor (R) inhibitors, IL-12/23 p40 inhibitors, and IL-23p19 inhibitors) [1,2,5,6].

7.2. SCIENTIFIC RATIONALE FOR THIS TRIAL

The phase III reSURFACE 2 base study lasted 52 weeks and aimed to assess the efficacy, safety and tolerability of tildrakizumab (SCH 900222/MK-3222), compared to placebo and etanercept, for the treatment of patients with moderate-to-severe chronic plaque psoriasis.

A subsequent extension of the reSURFACE2 long-term extension is currently in place to continue capturing long-term efficacy and safety data for this subset of patients who have received tildrakizumab for at least 5 years. According to the protocol of the trial (protocol number MK-3222-011), the study lasted until tildrakizumab was available in the country, or until December 2020, whichever came first.

Tildrakizumab became available in Poland on November 4th, 2019. At that point in time, patients did not longer continue receiving tildrakizumab in the context of the study. According to Polish criteria, patients should had a baseline Psoriasis Area and Severity Index (PASI) greater than 18 and a Dermatology life quality index (DLQI) greater than 10 and a Body surface area (BSA) greater than 10 in order to be entitled to treatment with a biologic therapies for psoriasis [7]. Considering these criteria, it was possible that patients discontinuing the tildrakizumab clinical trial might be left untreated (at least with regards to systemic therapies) for a certain period of time, until the disease progressively relapsed to an extent that required medical treatment again.

Tildrakizumab is a specific IL23p19 inhibitor. Published data suggests that, upon treatment discontinuation, the beneficial effects of treatment with IL23p19 inhibitors may persist over a certain period of time [8]. Considering the mechanism of action of tildrakizumab, and the fact that these patients would have received tildrakizumab for at least 5 years when the present study started, it is scientifically interesting to investigate the evolution of psoriasis over time once tildrakizumab is stopped. Additionally, the factors that condition the differences in the duration of remission obtained in clinical setting are not well understood. The expression of certain blood and skin inflammatory biomarkers may determine the disease course after treatment is discontinued.

8. STUDY OBJECTIVES

8.1. PRIMARY OBJECTIVE

- To describe blood and skin inflammatory biomarkers and its correlation with psoriasis disease severity over time after having discontinued long-term treatment with tildrakizumab

8.2. SECONDARY OBJECTIVES

- To assess time to disease relapse in the overall and in the different tildrakizumab responder populations

- To assess changes in disease status (PASI, BSA, Physician´s Global Assessment [PGA], nail PGA [nPGA], and scalp PGA [scPGA]) from baseline and until the End of Study (EoS)

- To assess changes in Patient Reported Outcomes (PROs) from baseline and until the EoS

9. INVESTIGATIONAL PLAN

9.1. OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This was a multicentre, interventional, prospective, phase IV clinical study. The main aim was to evaluate the psoriasis disease control over time in patients who had received tildrakizumab for at least the last 5 years and had discontinued it and to describe blood and skin inflammatory biomarkers and its correlation with disease relapse.

Patients started the present study after ending their participation in the reSURFACE2 study in Poland (protocol number MK-3222-011). The reSURFACE2 study lasted until tildrakizumab was available in the country. Tildrakizumab became available in Poland on November 4th, 2019. At that point in time, patients no longer continued receiving tildrakizumab in the context of the reSURFACE2 study.

Adult patients who had participated and completed this long-term extension of the reSURFACE 2 study might be eligible to be included in the present study. Overall, approximately 47 subjects from 3 centres from Poland were expected to be included. However, due to premature study termination only 9 subjects were included in 2 study centres.

Subjects did not receive any study medication during the study.

Further details about the study design are described in Section 9 of the clinical study protocol (CSP), listed in Appendix 16.1.1.

After a 6-month inclusion period, there were up to 9 scheduled visits planned, one every 12 weeks (up to 96 weeks):

- Visit 1: Baseline. Whenever possible 12 weeks after their last tildrakizumab dose in the reSURFACE 2 long-term extension (+ 2 weeks)

- Visit 2: Week 12 after baseline (+/- 1 week)

- Visit 3: Week 24 after baseline (+/- 1 week)

- Visit 4: Week 36 after baseline (+/- 1 week)

- Visit 5: Week 48 after baseline (+/- 1 week)

- Visit 6: Week 60 after baseline (+/- 1 week)

- Visit 7: Week 72 after baseline (+/- 1 week)

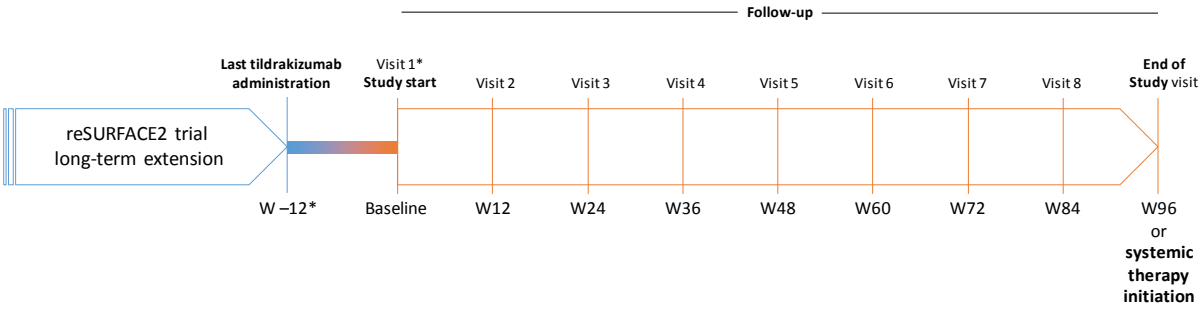
- Visit 8: Week 84 after baseline (+/- 1 week)

- EoS visit: Initiation of any systemic therapy for psoriasis or Week 96 after baseline (+/- 1 week), whatever occurred first.

Subjects were to remain in the study for 96 weeks or until they initiate any systemic therapy for psoriasis (including phototherapy), whichever occurred first.

The expected duration of the trial was 122 weeks, from Q4 2019 to Q2 2022. However, due to premature study termination the duration of the trial was of 31 weeks.

Figure 1. Trial Design



*Visit 1 was scheduled, whenever possible, 12 weeks after receiving the last tildrakizumab dose in the reSURFACE 2 study (+2 weeks).

Additionally, extra unscheduled visits due to psoriasis worsening could have been performed during the study, as deemed necessary by the subject and/or the investigator.

Systemic therapy initiation included phototherapy.

9.2. DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

There was no study treatment in this multicentre, interventional, prospective, phase IV clinical study and, consequently, no control group. Subjects were managed according to the best clinical practice, with additional scheduled blood testing and one skin biopsy.

Subjects attended the baseline visit 12 weeks after their last tildrakizumab dose in the reSURFACE 2 long-term extension, whenever possible.

Subjects remained in the study for 96 weeks or until they initiated any systemic therapy for psoriasis (including phototherapy).

9.3. SELECTION OF STUDY POPULATION

9.3.1. Inclusion criteria

Subjects eligible for inclusion in this study had to fulfil all of the following criteria:

1. Provide written informed consent prior to perform any study-related activity
2. Has participated in the long-term extension of the reSURFACE 2 study and has stopped tildrakizumab treatment once the extension finalizes

9.3.2. Exclusion criteria

Subjects fulfilling any of the following criteria were not eligible for inclusion in this study:

1. Subjects unable to comply with the requirements of the study
2. Subjects who in the opinion of the investigator should not participate in the study

9.4. TREATMENTS

9.4.1. Treatments administered

Despite the fact that during this study there was no scheduled administration of any investigational medicinal product, the study objectives aimed to investigate the effects of tildrakizumab after it was discontinued.

9.4.2. Identity of study drug

Not applicable.

9.4.3. Method of assigning subjects to treatment groups

Not applicable.

9.4.4. Selection of doses in the study

Not applicable.

9.4.5. Selection and timing of dose for each subject

Not applicable.

9.4.6. Blinding

Not applicable.

9.4.7. Prior and concomitant therapy

See Section 11.8 of the CSP, listed in Appendix 16.1.1.

9.4.8. Treatment compliance

Not applicable.

9.4.9. Early study termination

According to Appendix 16.1.1-Protocol-Section 10.6, Almirall reserves the right to prematurely terminate (i.e., suspend) the study. This could include the following reasons:

- The Principal Investigator/Coordinating Investigator and the Sponsor feel that the type, number and /or severity of AEs justify discontinuation of the trial.
- The sponsor decides to discontinue the study.

The reason for premature termination of this study is detailed below:

Due to the inability to recruit enough patients within the time frame established, Almirall decided on 31 July 2020 to early terminate this study. The Clinical Research Organization (CRO) informed the investigators in detail about the procedures to follow for the subjects enrolled in the study (e.g completion of the eCRF, schedule of close out visits, etc.) and investigational teams were in charge of informing the study subjects.

Following the protocol, after the prematurely termination of the trial, the subjects attempted to complete the study assessments included in the EoS visit. Subjects had not received any IMP within this clinical trial, so no change in patient medication was necessary.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. Efficacy and safety measurements assessed and flow chart

9.5.1.1 Primary Endpoint

- Blood and skin inflammatory biomarkers (YES [presence of inflammatory biomarkers]/NO [no presence of inflammatory biomarkers]) at each visit

- Proportion of patients with psoriasis relapse during the 96-week follow-up period (YES [relapse]/ NO [disease control]), where relapse is defined using the following thresholds:

    - PASI >3* (in patients who had a PASI ≤3 at baseline)
    - PASI >5* (in patients who had a PASI ≤5 at baseline)
    - DLQI >5* (in patients who had a DLQI ≤5 at baseline)
    - Initiation of any topical drug/medication for psoriasis†^
    - Initiation of any systemic therapy for psoriasis (biologic or non-biologic)†

*Only to be considered at first occurrence

†To be considered at every occurrence

^Only apply to topical drugs/medications (not soaps, shampoos, emollients, keratolytics, etc. will be included in this group)

9.5.1.2 Secondary Endpoints

Efficacy endpoints

- Time to relapse during the 96-week follow-up period, defining relapse as the above mentioned categories

- Absolute PASI score and change from baseline in the absolute PASI score over time, from baseline EoS visit

- Absolute BSA score and change from baseline in the absolute BSA score over time, from baseline to EoS visit

- Absolute DLQI and DLQI-R (Dermatology life quality index – modified scoring) scores and change from baseline in the absolute DLQI and DLQI-R scores over time, from baseline to EoS visit

- Absolute PGA, nPGA and scPGA scores and change in the absolute PGA, nPGA and scPGA scores over time, from baseline to EoS visit

- Absolute pain- and pruritus- Numeric Rating Scale (NRS) scores and change from baseline in the absolute pain- and pruritus-NRS scores over time, from baseline to EoS visit

Safety and tolerability endpoints

Safety outcomes included adverse events (AEs), physical examination, vital signs, and clinical laboratory assessments (haematology and biochemistry).

9.5.1.3 Flow-chart of Study Procedures

The flow chart is described in Section 3.1 of the CSP, listed in Appendix 16.1.1.

9.5.1.4 Scheduled activities and Study Visits

Written and personally dated informed consent were obtained from the subject before any study specific procedures took place.

The trial design is described in Figure 1. The recording and reporting of AEs are described in detail in sections 12.3 (Schedule activities and trial visits) and 12.7 (Adverse Events) of the CSP, listed in Appendix 16.1.1.

9.5.2. Appropriateness of measurements

Standardized methods for measurements of efficacy and safety variables were used. The Investigator assessment instruments and PROs were accepted standards for clinical evaluation. The laboratory analyses were performed by central laboratories using validated assays.

9.6. DATA QUALITY ASSURANCE

Details about data quality assurance are described in Section 15 of the CSP, listed in Appendix 16.1.1.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1. Statistical and analytical plans

A fully specified statistical analysis plan (SAP), which provide the technical details of the statistical analysis outlined below, was prepared, approved, and dated 7 October 2020. Detailed information on the statistical methods planned can be found in SAP, listed in Appendix 16.1.9.

9.7.2. Data sets to be analyzed

Due to the early termination of the study, there was only one statistical analysis population:

- The **Full Analysis Set (FAS)** was defined as all patients who attended baseline visit and received a patient number.

A Per Protocol population (PP) was also defined in the protocol, although due to the limited number of subjects included in this study none of the statistical evaluations were repeated for the PP.

9.7.3. Analysis of Main Study Variables

The statistical approach for the analysis of primary and secondary variables is described below. Further specification of the analyses can be found in Appendix 16.1.9.

Due to the early termination of the study, the analyses defined in the SAP have been changed and adapted from the CSP:

- Primary and some secondary objectives (relapse during the 96-week follow-up period and time to relapse) were impossible to asses because there were no data collected.
- Other objectives as changes from baseline or shift tables for laboratory values, vital signs or physical examination were removed from the analysis because there were not enough data collected in the study.

9.7.4. Determination of sample size

Up to 47 subjects completing the long-term extension of the reSURFACE 2 study were planned to be included in the study. Since this was an exploratory trial, no formal sample size calculation was performed, and 47 subjects were considered enough to meet the objectives of the trial.

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. Changes to the conduct of the study

All changes made to the CSP were documented as four amendments that are summarized below together with their corresponding justification. Full amendments can be found in Appendix 16.1.1

9.8.1.1 Non-substantial Amendment number 1 to the protocol (31 October 2019)

In this amendment, the following changes were carried out:

- Clarification and further definition of the additional laboratory assessments and the sampling management (section 12.8.5).
- Photographs taken during the study were redefined.
- Update of the expected availability date of tildrakizumab in Poland.
- Update of the definition of EoS visit requirement in Section 12.3.5.
- Clarification of the primary variable, as inflammatory biomarkers were not going to be assessed at each study visit (“each applicable visit” added).
- Removal of the requirement of patients having to present nail/scalp psoriasis to measure nail/scalp PGA.
- Removal of the requirement of body temperature measurement to be axillary.
- The PRO data collection method was updated
- Minor changes (e.g. typo) were also included.

9.8.1.2 Substantial Amendment number 2 to the protocol (7 November 2019)

In this amendment, the main changes were:

- Clarification that the last dose of tildrakizumab received by the patient was no longer necessary to be administered during the feeder reSURFACE 2 study.
- The patients were no longer screened during the last visit of the feeder reSURFACE 2 study.
- There was an additional skin biopsy during the study (at Visit 5 or EoS visit, whichever occurred first).

9.8.1.3 Non-substantial Amendment number 3 to the protocol (10 January 2020)

This amendment included the following changes:

- Clarification that patients were enrolled in this study during the 20 weeks wash-out period of the feeder reSURFACE 2 study.
- Further definition of the location of biopsy sampling and photography taking.
- Update of the expected study-associated dates.
- Minor changes (e.g. typo) were also included.

9.8.1.4 Substantial Amendment number 4 to the protocol (3 April 2020)

In this amendment, the main changes were:

- Implementation of the following 3 measures aiming to reduce potential safety risks for patients during the COVID-19 pandemic situation:
    1) Allow the possibility of delaying the Baseline and/or EoS visits due to the COVID-19 pandemic situation.
    2) Allow the Study visits 2-8 to either be performed as remote (telephone) visits whenever the on-site visit was not feasible or to be skipped (not performed) whenever neither on-site nor remote visit were feasible due to the COVID-19 pandemic situation
    3) Extend the Study visits 2-8 and EoS visit window from +/-1 week to +/- 2 weeks during the COVID-19 pandemic situation

- Clarification that the biopsies were optional.
- Update of Almirall personnel.

10. STUDY SUBJECTS

10.1. DISPOSITION OF SUBJECTS

At the time of the premature termination of this study, 9 subjects at two centres had signed the ICF. Of these subjects, none of them completed the study. Reasons for exclusion or discontinuation of the study are described below (Table 1 and Listing 16.2.1):

- Four subjects (subject 1001-101, 1001-104, 1001-105 and 1001-106) discontinued the study due to 'withdrawal by subject'.
- Five subjects (subject 1001-102, 1001-103, 1003-101, 1003-102 and 1003-103) discontinued the study due to 'study terminated by sponsor'.

Table 1. Subject disposition and study populations

		FAS (N=9)
Screened		9 (100.0%)
Study completed		0 (0.0%)
Study Discontinued	Study terminated by sponsor	5 (55.6%)
Study Discontinued	Withdrawal by subject	4 (44.4%)
Full Analysis Set		9 (100.0%)
Per-Protocol Set		5 (55.6%)
Full analysis set (FAS): all patients who attended baseline visit and received a patient number Per Protocol Set (PPS): all patients in the screened population who met all inclusion/exclusion criteria and did not have any major protocol violation		

Source data: Table 14.1.1

10.2. PROTOCOL DEVIATIONS

A total of 4 subjects (44.4%) presented major protocol deviations during the study. The biological samples of 3 subjects (33.3%) were improperly managed and 1 subject (11.1%) was included in the study 3 days before required 12 weeks period after last tildrakizumab dose.

All protocol deviations recorded in the study are listed in Listing 16.2.2.

11. EFFICACY EVALUATIONS

11.1. DATA SETS ANALYSED

All 9 included subjects attended the baseline visit and therefore were included in the FAS population. Of these 9 subjects, 4 subjects (44.4%) had major protocol deviations and were not included in the PP population. None of the 9 subjects completed the study (Table 1).

11.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

11.2.1. Demographics

A total of 7 subjects (77.8%) were male, and all of them were white. At screening visit, subjects had a mean (standard deviation [SD]) age of 47.4 (11.8) years and a mean (SD) body mass index (BMI) of 29.3 (5.7) kg/cm^2. Mean (SD) waist circumference was 104.3 (15.6) cm and mean (SD) waist to hip ratio was 1.0 (0.1) cm/cm. None of the subjects had fever at screening visit (mean [SD] temperature of 36.5 [0.14] ºC; maximum of 36.8 ºC) (Table 2 and Listings 16.2.4.2, 16.2.7.3 and 16.2.7.5).

Table 2. Demographic data at baseline visit

Variable	Statistics		FAS (N=9)
Age	No. of obs.		9
	Mean (SD)		47.4 (11.8)
	Standard error of mean		3.94
	95% CI		[38.3, 56.5]
	Median		46.0
	Q1, Q3		38.0, 56.0
	Min, Max		31, 67
Sex	n (%)	Female	2 (22.2%)
	n (%)	Male	7 (77.8%)
Race	n (%)	White	9 (100.0%)
BMI (Kg/m^2)	No. of obs.		9
	Mean (SD)		29.29 (5.70)
Waist circumference (cm)	No. of obs.		9
	Mean (SD)		104.3 (15.6)
Waist-hip ratio (cm/cm)	No. of obs.		9
	Mean (SD)		0.983 (0.091)
Body Temperature (degree Celsius)	No. of obs.		9
	Mean (SD)		36.50 (0.14)
	Min, Max		36.4, 36.8

Source data: Based on Tables 14.1.5, 14.1.7.2 and 14.1.8

BMI; body mass index; n, number of subjects in each category; SD, standard deviation

11.2.2. Medical History

The most frequent relevant medical condition by System Organ Class (SOC) were cardiac disorders, endocrine disorders, metabolism and nutrition disorders, respiratory, thoracic and mediastinal disorders

and vascular disorders (2 subjects [22.2%] in each category) (Section 14, Table 14.1.6.1 and Listing 16.2.4.3).

Only 1 subject (11.1%) was regular smoker at baseline, while 5 subjects (55.6%) had never smoked. One subject (11.1%) consumed alcohol in a regular basis and 5 subjects (55.6%) drank alcohol occasionally (Section 14, Table 14.1.6.2 and Listing 16.2.4.4).

11.2.3. Disease history

At baseline visit, mean (SD) time since diagnosis of psoriasis was 25.9 (11.8) years. At the time of diagnosis, eight subjects (88.9%) were diagnosed of plaque psoriasis and one subject (11.1%) of guttate psoriasis. Current psoriasis type at baseline visit was plaque psoriasis in 8 subjects (88.9%) and psoriatic arthritis in 1 subject (11.1%), with a severity of '0%' and 'less than 10%' of involved area in 4 (44.4%) and 5 (55.6%) subjects, respectively. Two subjects (22.2%) were diagnosed of psoriatic arthritis with a mean (SD) time since diagnosis of 15.5 (6.4) years. One subject (11.1%) reported nail psoriasis and two subjects (22.2%) reported scalp psoriasis. Mean (SD) time since last relapse was 1669.4 (1298.7) days (Table 3 and Listing 16.2.4.5).

Table 3. Medical history at baseline visit. Psoriasis history

Variable	Statistics		FAS (N=9)
Fitzpatrick skin type or phototype	n (%)	I	0 (0.0%)
		II	8 (88.9%)
		III	1 (11.1%)
		IV	0 (0.0%)
		V	0 (0.0%)
		VI	0 (0.0%)
Time to psoriasis diagnosis (years)	No. of obs.		9
	Mean (SD)		25.9 (11.8)
	Standard error of mean		3.93
	95% CI		[16.8, 34.9]
	Median		24.0
	Q1, Q3		16.0, 33.0
	Min, Max		11, 44
Type of psoriasis when diagnosed	n (%)	Plaque	8 (88.9%)
		Guttate	1 (11.1%)
		Inverse	0 (0.0%)
		Pustular	0 (0.0%)
		Erythrodermic	0 (0.0%)
		Psoriatic arthritis	0 (0.0%)
		Generalized pustular	0 (0.0%)
		Impetigo herpetiformis	0 (0.0%)
Current psoriasis type(s)	n (%)	Plaque	8 (88.9%)
		Guttate	0 (0.0%)
		Inverse	0 (0.0%)
		Pustular	0 (0.0%)
		Erythrodermic	0 (0.0%)

Variable	Statistics		FAS (N=9)
		Psoriatic arthritis	1 (11.1%)
		Generalized pustular	0 (0.0%)
		Impetigo herpetiformis	0 (0.0%)
Current psoriasis severity	n (%)	0% of involved area	4 (44.4%)
		less than 10% of involved area	5 (55.6%)
		10 to 29% of involved area	0 (0.0%)
		30 to 49% of involved area	0 (0.0%)
		50 to 69% of involved area	0 (0.0%)
		70 to 89% of involved area	0 (0.0%)
Current psoriasis severity	n (%)	90 to 100% of involved area	0 (0.0%)
Psoriatic Arthritis	n (%)	No	7 (77.8%)
		Yes	2 (22.2%)
Time to Psoriatic Arthritis diagnosis (years)	No. of obs.		2
	Mean (SD)		15.5 (6.4)
	Standard error of mean		4.50
	95% CI		[-41.7, 72.7]
	Median		15.5
	Q1, Q3		11.0, 20.0
	Min, Max		11, 20
Nail psoriasis	n (%)	No	8 (88.9%)
		Yes	1 (11.1%)
Scalp psoriasis	n (%)	No	7 (77.8%)
		Yes	2 (22.2%)
Time to last relapse (days)	No. of obs.		9
	Mean (SD)		1669.4 (1298.7)
	Standard error of mean		432.88
	95% CI		[671.2, 2667.7]
	Median		2201.0
	Q1, Q3		106.0, 2228.0
	Min, Max		24, 3701
Partial dates of the last relapse imputed as follow: missing day - imputed the 1st of the month, missing day and month - imputed 1st January			

Source data: Table 14.1.6.3

n, number of subjects in each category; SD, standard deviation.

11.2.4. Information from reSURFACE 2 trial

Information of the reSURFACE 2 trial is provided in Table 4 and in Listing 16.2.4.6.

At baseline visit, the mean (SD) time since last dose of tildrakizumab within the reSURFACE 2 study was 84.2 (1.4) days. Four (44.4%) subjects received the 100 mg dose of tildrakizumab during the long-term safety extension (arm B) and 5 (55.6%) subjects received the 200 mg dose (arm A).

The mean (SD) PASI score at baseline of the reSURFACE 2 trial was 18.3 (5.8), indicating a severe disease. The PASI score decreased during the reSURFACE 2 trial, with a mean (SD) score of 5.3 (5.5) at week 28 and 2.7 (2.0) at week 52. At last visit, mean (SD) PASI score was 2.5 (3.7).

Mean body surface area (BSA) score, PGA and DLQI also decreased during the reSURFACE 2 trial. At baseline, mean (SD) BSA score was 30.8 (12.4); at week 28, 1.5 (2.3) and at last visit 1.3 (2.4). Mean (SD) PGA score at baseline was 3.2 (0.4), and at last visit 1.1 (0.8). Mean (SD) DLQI score at baseline was 12.8 (8.8) and at last visit 0.0 (0.0).

The proportion of PASI responders to tildrakizumab increased during the reSURFACE 2 trial. At week 28, 5 (55.6%) subjects were PASI responders (≥75% improvement in PASI score) and 3 (33.3%) subjects were partial responders. Only 1 (11.1%) subject did not respond to tildrakizumab. At week 52, 2 (22.2%) and 7 (77.8%) subjects were partial responders and responders, respectively; and at last visit, 1 (11.1%) and 7 (77.8%) subjects were partial-responders and responders, respectively.

Regarding the number of subjects reporting relapse episodes in the last year of the reSURFACE 2 trial, 6 (66.7%) subjects reported no relapse episodes and 3 (33.3%) subjects 1 relapse episode.

Table 4. reSURFACE2 trial information. Descriptive statistics.

Variable	Statistics		FAS (N=9)
Time to last dose of tildrakizumab within the reSURFACE 2 study (days)	No. of obs.		9
	Mean (SD)		84.2 (1.4)
	Standard error of mean		0.46
	95% CI		[83.2, 85.3]
	Median		84.0
	Q1, Q3		84.0, 85.0
	Min, Max		81, 86
Dose of tildrakizumab received during the long-term safety extension	n (%)	100 mg	4 (44.4%)
		200 mg	5 (55.6%)
Arm in the reSURFACE 2 trial	n (%)	A: tildrakizumab 200 mg	5 (55.6%)
		B: tildrakizumab 100 mg	4 (44.4%)
		C: placebo	0 (0.0%)
		D: etanercept	0 (0.0%)
PASI score at Baseline	No. of obs.		9
	Mean (SD)		18.26 (5.80)
	Standard error of mean		1.932
	95% CI		[13.80, 22.71]
	Median		16.30
	Q1, Q3		14.40, 19.30
	Min, Max		13.2, 31.5
PASI score at Week 28	No. of obs.		9
	Mean (SD)		5.31 (5.53)
	Standard error of mean		1.842
	95% CI		[1.06, 9.56]
	Median		4.50
	Q1, Q3		0.90, 6.60

Variable	Statistics		FAS (N=9)
	Min, Max		0.0, 15.1
PASI score at Week 52	No. of obs.		9
	Mean (SD)		2.74 (2.02)
	Standard error of mean		0.672
	95% CI		[1.19, 4.29]
	Median		2.40
	Q1, Q3		1.90, 3.90
	Min, Max		0.0, 5.9
PASI score at Last visit	No. of obs.		9
	Mean (SD)		2.47 (3.69)
	Standard error of mean		1.231
	95% CI		[-0.37, 5.30]
	Median		1.20
	Q1, Q3		0.20, 1.80
	Min, Max		0.0, 11.0
BSA score at Baseline	No. of obs.		9
	Mean (SD)		30.8 (12.4)
	Standard error of mean		4.12
	95% CI		[21.3, 40.3]
	Median		27.0
	Q1, Q3		22.0, 44.0
	Min, Max		15, 48
BSA score at Week 28	No. of obs.		6
	Mean (SD)		1.52 (2.33)
	Standard error of mean		0.952
	95% CI		[-0.93, 3.96]
	Median		0.05
	Q1, Q3		0.00, 4.00
	Min, Max		0.0, 5.0
BSA score at Week 52	No. of obs.		6
	Mean (SD)		2.33 (2.82)
	Standard error of mean		1.151
	95% CI		[-0.62, 5.29]
	Median		1.25
	Q1, Q3		0.00, 5.70
	Min, Max		0.0, 5.8
BSA score at Last visit	No. of obs.		6
	Mean (SD)		1.33 (2.36)
	Standard error of mean		0.963

Variable	Statistics		FAS (N=9)
	95% CI		[-1.14, 3.81]
	Median		0.25
	Q1, Q3		0.00, 1.50
	Min, Max		0.0, 6.0
PGA score at Baseline	No. of obs.		9
	Mean (SD)		3.2 (0.4)
	Standard error of mean		0.15
	95% CI		[2.9, 3.6]
	Median		3.0
	Q1, Q3		3.0, 3.0
	Min, Max		3, 4
PGA score at Week 28	No. of obs.		9
	Mean (SD)		1.6 (0.9)
	Standard error of mean		0.29
	95% CI		[0.9, 2.2]
	Median		2.0
	Q1, Q3		1.0, 2.0
	Min, Max		0, 3
PGA score at Week 52	No. of obs.		9
	Mean (SD)		1.1 (0.8)
	Standard error of mean		0.26
	95% CI		[0.5, 1.7]
	Median		1.0
	Q1, Q3		1.0, 2.0
	Min, Max		0, 2
PGA score at Last visit	No. of obs.		9
	Mean (SD)		1.1 (0.8)
	Standard error of mean		0.26
	95% CI		[0.5, 1.7]
	Median		1.0
	Q1, Q3		1.0, 2.0
	Min, Max		0, 2
DLQI score at Baseline	No. of obs.		6
	Mean (SD)		12.8 (8.8)
	Standard error of mean		3.60
	95% CI		[3.6, 22.1]
	Median		10.0
	Q1, Q3		8.0, 13.0
	Min, Max		6, 30

Variable	Statistics		FAS (N=9)
DLQI score at Week 28	No. of obs.		6
	Mean (SD)		2.2 (2.6)
	Standard error of mean		1.05
	95% CI		[-0.5, 4.9]
	Median		2.0
	Q1, Q3		0.0, 2.0
	Min, Max		0, 7
DLQI score at Week 52	No. of obs.		6
	Mean (SD)		3.8 (4.1)
	Standard error of mean		1.66
	95% CI		[-0.4, 8.1]
	Median		3.5
	Q1, Q3		0.0, 5.0
	Min, Max		0, 11
DLQI score at Last visit	No. of obs.		3
	Mean (SD)		0.0 (0.0)
	Standard error of mean		0.00
	95% CI		[0.0, 0.0]
	Median		0.0
	Q1, Q3		0.0, 0.0
	Min, Max		0, 0
PASI response to tildrakizumab at week 28	n (%)	<50% improvement in PASI score (non-responder)	1 (11.1%)
		=>50% to <75% improvement in PASI score (partial-responder)	3 (33.3%)
		=>75% improvement in PASI score (responder)	5 (55.6%)
PASI response to tildrakizumab at week 52	n (%)	=>50% to <75% improvement in PASI score (partial-responder)	2 (22.2%)
		=>75% improvement in PASI score (responder)	7 (77.8%)
PASI response to tildrakizumab at last visit performed in the reSURFACE 2 trial	n (%)	=>50% to <75% improvement in PASI score (partial-responder)	1 (11.1%)
		=>75% improvement in PASI score (responder)	8 (88.9%)
Number of relapse episodes in the last year	n (%)	0	6 (66.7%)
		1	3 (33.3%)

Source data: Table 14.1.9

n, number of subjects in each category; SD, standard deviation

11.2.5. PASI, BSA, PGA, nPGA, scPGA, DLQI, DLQI-R, Pruritus NRS and Pain NRS at baseline

The scores of PASI, BSA, PGA, nPGA, scPGA, DLQI, DLQI-R, Pruritus NRS and Pain NRS at baseline are described in Table 5 and in Listings 16.2.5.1 – 16.2.5.7.

The mean (SD) PASI and BSA score at baseline were 1.5 (2.1) and 1.0 (2.0), respectively, indicating a mild severity of the disease and a low area of the body affected by psoriasis.

There were no subjects with a PGA score of 3, 4 or 5 at baseline. The mean (SD) PGA score at baseline was 0.7 (0.7), with subjects presenting a PGA score of 0 (n=4), 1 (n=4) or 2 (n=1).

nPGA and scPGA scores were assessed only in subjects with nail and scalp psoriasis, respectively. At baseline, six out of 9 subjects (66.7%) reported nail psoriasis with a mean (SD) nPGA score of 0.2 (0.4) (nPGA score of 0 [n=5] or 1 [n=1]). Likewise, 6 subjects (66.7%) indicated a scalp involvement with a mean (SD) scPGA score of 0.5 (0.8) (scPGA score of 0 [n=4], 1 [n=1] or 2 [n=1]).

Regarding PROs, at baseline, subjects had a mean (SD) DLQI and DLQI-R score of 1.6 (2.3). The DLQI score ranges from a maximum of 30 to a minimum of 0, being the higher the score, the more impaired quality of life. Therefore, a score close to 0 indicates a small effect on subject's quality of life.

Finally, subjects reported a mean (SD) pruritus NRS of 0.8 (1.1) and a mean (SD) NRS pain of 0.3 (0.7), which reflects a low intensity of pruritus and pain.

Table 5. PASI, BSA, DLQI, DLQI-R, Pruritus NRS, Pain NRS, PGA, nPGA and scPGA at baseline. Descriptive statistics.

Assessment	Statistics	FAS (N=9)
PASI	No. of obs.	9
	Mean (SD)	1.46 (2.07)
	Standard error of mean	0.689
	95% CI	[-0.13, 3.05]
	Median	0.60
	Q1, Q3	0.00, 1.80
	Min, Max	0.0, 6.0
BSA	No. of obs.	9
	Mean (SD)	1.00 (1.95)
	Standard error of mean	0.649
	95% CI	[-0.50, 2.50]
	Median	0.10
	Q1, Q3	0.00, 0.90
	Min, Max	0.0, 6.0
DLQI	No. of obs.	9
	Mean (SD)	1.6 (2.3)
	Standard error of mean	0.77
	95% CI	[-0.2, 3.3]
	Median	1.0
	Q1, Q3	0.0, 1.0
	Min, Max	0, 6
DLQI-R	No. of obs.	9
	Mean (SD)	1.6 (2.3)
	Standard error of mean	0.76
	95% CI	[-0.2, 3.3]

Assessment	Statistics	FAS (N=9)
	Median	1.0
	Q1, Q3	0.0, 1.1
	Min, Max	0, 6
Pruritus NRS	No. of obs.	9
	Mean (SD)	0.8 (1.1)
	Standard error of mean	0.36
	95% CI	[-0.1, 1.6]
	Median	0.0
	Q1, Q3	0.0, 1.0
	Min, Max	0, 3
Pain NRS	No. of obs.	9
	Mean (SD)	0.3 (0.7)
	Standard error of mean	0.24
	95% CI	[-0.2, 0.9]
	Median	0.0
	Q1, Q3	0.0, 0.0
	Min, Max	0, 2
PGA (continuous)	No. of obs.	9
	Mean (SD)	0.7 (0.7)
	Standard error of mean	0.24
	95% CI	[0.1, 1.2]
	Median	1.0
	Q1, Q3	0.0, 1.0
	Min, Max	0, 2
PGA (categorical)	Cleared	4 (44.4%)
	Minimal	4 (44.4%)
	Mild	1 (11.1%)
	Moderate	0 (0.0%)
	Marked	0 (0.0%)
	Severe	0 (0.0%)
nPGA (continuous)	No. of obs.	6
	Mean (SD)	0.2 (0.4)
	Standard error of mean	0.17
	95% CI	[-0.3, 0.6]
	Median	0.0
	Q1, Q3	0.0, 0.0
	Min, Max	0, 1
nPGA (categorical)	Missing	3 (33.3%)
	Clear	5 (55.6%)
	Almost Clear	1 (11.1%)
	Mild	0 (0.0%)
	Moderate	0 (0.0%)
	Severe	0 (0.0%)
scPGA (continuous)	No. of obs.	6
	Mean (SD)	0.5 (0.8)

Assessment	Statistics	FAS (N=9)
	Standard error of mean	0.34
	95% CI	[-0.4, 1.4]
	Median	0.0
	Q1, Q3	0.0, 1.0
	Min, Max	0, 2
scPGA (categorical)	Missing	3 (33.3%)
	Clear	4 (44.4%)
	Almost Clear	1 (11.1%)
	Mild	1 (11.1%)
	Moderate	0 (0.0%)
	Severe	0 (0.0%)

Source data: Based on Tables 14.1.11 - 14.1.15 and 14.2.5.1-14.2.5.3

n, number of subjects in each category; SD, standard deviation

11.3. MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable.

11.4. EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1. Analysis of efficacy

11.4.1.1 Primary Efficacy Analysis

11.4.1.1.1 Blood and skin inflammatory biomarkers and psoriasis relapse during the follow-up period

The primary efficacy variable 'blood and skin inflammatory biomarkers' was not evaluated because blood biomarkers were not analysed and none of the included subjects granted permission for skin biopsies.

Regarding the proportion of subjects with psoriasis relapse, 4 (44.4%) subjects reported psoriasis relapse during the 24-weeks of follow-up period (Table 6).

Table 6. Proportion of subjects with psoriasis relapse during the follow-up period. Descriptive statistics.

	Statistics	FAS (N=9)
Psoriasis relapse during the follow-up period	No	5 (55.6%)
Psoriasis relapse during the follow-up period	Yes	4 (44.4%)
Relapse is defined using the following thresholds: - PASI >3 (in patients who had a PASI <=3 at baseline) - PASI >5 (in patients who had a PASI <=5 at baseline) - DLQI >5 (in patients who had a DLQI <=5 at baseline) - Initiation of any topical drug/medication for psoriasis - Initiation of any systemic therapy for psoriasis (biologic or non-biologic)		

Source data: Table 14.2.1

11.4.1.2 Secondary Efficacy Analysis

The secondary efficacy variables were not evaluated because there were no data collected for some secondary objectives and because due to the early termination of the study only 9 subjects (of the 47 subjects planned) were included and none of the subjects reached the 96 weeks of follow-up. Description of the planned secondary efficacy analysis of these 9 subjects are shown in Section 14 (Table 14.2.2-Table 14.2.7).

Last assessment of PASI, BSA, PGA, nPGA and scPGA scores were at week 24.

Mean (SD) absolute PASI score at week 24 (n=3) was 5.63 (2.98) and mean (SD) change from baseline 2.27 (1.15). Regarding BSA, mean (SD) score at week 24 (n=3) was 3.33 (4.06) with a mean (SD) change from baseline of 1.00 (0.87).

PGA score had a mean (SD) value of 1.7 (0.6) at week 24 (n=3), and a mean (SD) change from baseline of 0.3 (0.6). Last mean (SD) assessment of nPGA was 1.7 (1.2) (n=3) and mean (SD) change from baseline was 1.3 (0.6). Likewise, mean (SD) scPGA score was 1.0 (1.0) (n=3) at week 24 with a mean (SD) change from baseline of 0.3 (0.6).

DLQI, DLQI-R, pain-NRS and pruritus-NRS were assessed at EoS. Mean (SD) DLQI score at EoS was 11.0 (4.2) (n=2), with a mean (SD) change from baseline of 8.0 (8.5). Regarding DLQI-R, mean (SD) score at EoS was 13.8 (5.3) (n=2) and mean (SD) change from baseline was 10.8 (9.5).

Mean (SD) pain-NRS score at EoS and change from baseline were the same, 4.5 (3.5) (n=2), respectively. Similarly, mean pruritus-NRS score at EoS and change from baseline were 4.5 (0.7) (n=2), respectively.

11.4.2. Statistical/analytical issues

Not applicable.

11.4.3. Tabulation of individual response data

Individual Response Data are listed in Appendix 16.2.

11.4.4. Drug dose, drug concentration, and relationships to response (if applicable)

Not applicable.

11.4.5. Drug-drug and drug disease interactions

Not applicable.

11.4.6. By-subject displays

Individual subject data generated from clinical database for all subjects are provided in Appendix 16.2.

11.4.7. Efficacy conclusions

Due to the early study termination, only 9 subjects were screened, and none of them could finalize the 96 weeks of follow up. Therefore, the evolution of psoriasis over time once tildrakizumab is stopped could not be analyzed. As a result, there are no efficacy conclusions.

12. SAFETY EVALUATION

12.1. EXTENT OF EXPOSURE

Not applicable.

12.2. ADVERSE EVENTS (AEs)

12.2.1. Brief summary of adverse events

Throughout the study, 4 out of 9 subjects (44.4%) reported a total of 7 AEs. Six of the 7 AEs were of mild severity and 1 was moderate. No fatal or serious AEs (SAEs) were reported (Table 7 and Listing 16.2.6).

Table 7. Summary of AEs: Number of subjects with AEs, with non-AES, serious AEs, with serious non-AEs, AEs leading to study discontinuation and fatal AEs.

	FAS (N=9)
Number of adverse events	7
Number of patients with at least one adverse event	4 (44.4%)
Number of patients with no adverse event	5 (55.6%)
Number of serious adverse events	0
Number of patients with at least one serious adverse event	0 (0.0%)
Number of patients with no serious adverse event	9 (100.0%)
Number of fatal adverse events	0
Number of patients with at a fatal adverse event	0 (0.0%)

Source data: Table 14.3.1.1

12.2.2. Display of adverse events

Table 8 shows AE rates classified by SOC and PT. The most commonly affected SOC was skin and subcutaneous tissue disorders in 3 subjects (33.3%) (n=4 AEs; PT: psoriasis in 33.3% [N=3 subjects, 3 AEs] and PT: alopecia in 11.1% [N=1 subject, 1 AE]). Other SOCs affected were metabolism and nutrition disorders (11.1%), nervous system disorders (11.1%) and surgical and medical procedures (11.1%).

Table 8. Number and percentage of subjects with any adverse event (AE) and number of AE occurrences by System Organ Class (SOC), preferred term (PT).

	FAS (N=9)	
SYSTEM ORGAN CLASS/ Preferred term	No. of subjects	No. of events
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (33.3%)	4
Alopecia	1 (11.1%)	1
Psoriasis	3 (33.3%)	3
METABOLISM AND NUTRITION DISORDERS	1 (11.1%)	1
Dyslipidaemia	1 (11.1%)	1
NERVOUS SYSTEM DISORDERS	1 (11.1%)	1
Radiculopathy	1 (11.1%)	1
SURGICAL AND MEDICAL PROCEDURES	1 (11.1%)	1
Uterine dilation and curettage	1 (11.1%)	1
MedDRA text from version 22.1		

Source data: Table 14.3.1.2

12.2.3. Analysis of adverse events

A total of 7 AEs were reported in 4 (44.4%) subjects, of which one was of moderate severity (exacerbation of psoriasis) and 6 were of mild severity (radiculitis [n=1], hair loss [n=1], uterine dilation and curettage [n=1], dyslipidemia [n=1] and exacerbation of psoriasis [n=2]). None of the AEs was serious, fatal or led to discontinuation of the study.

12.2.4. Listing of adverse events

All AEs by subject, SOC and PT are listed in Appendix 16.2 (Listings 16.2.6).

12.3. DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1. Listing of deaths, other serious adverse events and other significant adverse events

12.3.1.1 Deaths

No deaths were reported.

12.3.1.2 Other Serious Adverse Events

No SAEs were reported.

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2. Narratives of deaths, other serious adverse events and certain other significant adverse events

Not applicable.

12.3.3. Analysis and discussion of deaths, other serious adverse events and certain other significant adverse events

Not applicable.

12.4. CLINICAL LABORATORY EVALUATION

12.4.1. Listing of individual laboratory measurements by subject and each abnormal laboratory value

Listings of individual laboratory test results by subject are provided in Appendix 16.2.8.

12.4.2. Evaluation of each laboratory parameter

12.4.2.1 Laboratory values Over Time

Laboratory tests were only performed at baseline so no changes over time were evaluated.

12.4.2.2 Individual Subject Changes.

Laboratory tests were only performed at baseline so no changes over time were evaluated.

12.4.2.3 Individual Clinically Significant Abnormalities

Laboratory tests were only performed at baseline so no changes over time were evaluated.

12.5. VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

12.5.1. Physical findings

No relevant changes were observed between baseline visit and week 24 except on dermatological examination. At baseline, 44.4% (n=4) of patients had a normal dermatological examination and 55.6% (n=5) abnormal not clinically significant dermatological examination. At week 24, all patients (n=3) had abnormal not clinically significant dermatological examination.

A summary of physical examination from baseline to EoS visit and by subject are provided in Section 14, Tables 14.3.3.1 and 14.3.3.2. Listings of physical examination by subject are provided in Appendix 16.2.8.

12.5.2. Vital signs

No relevant changes were observed in vital signs from baseline visit to EoS. A summary of vital sign parameters from baseline to EoS visit and by subject are provided in Section 14, Table 14.3.4.1. Listings of vital sign parameters by subject are provided in Appendix 16.2.8.

12.5.3. Prior and Concomitant Medication/Therapy

A total of 6 subjects (66.7%) used prior medications. Prior medications used were immunosuppressants (tildrakizumab [66.7%]) and antibacterials for systemic use (amoxicillin; clavulanic acid [11.1%], azithromycin [11.1%] and ciprofloxacin [11.1%]) (Section 14, Table 14.3.6.1 and Table 14.3.6.2).

Five subjects (55.6%) took concomitant medications during the study. The most used concomitant medications (>40% of the subjects) were antipsoriatics (44.4%; mainly betamethasone; calcipotriol [22.2%]); and corticosteroids, dermatological preparations (44.4%) (Section 14, Table 14.3.6.3 and Listing 16.2.4.7).

12.6. SAFETY CONCLUSIONS

Throughout the study, 4 subjects reported a total of 7 AEs. Almost all of them were of mild severity and none of them led to discontinuation of the study.

There were no deaths or SAEs reported during the study.

13. DISCUSSION AND OVERALL CONCLUSIONS

This was a phase IV study that aimed to evaluate the disease-modifying effect of long-term treatment with tildrakizumab in adult patients with moderate-to-severe plaque psoriasis. The study was terminated prematurely with 9 subjects included at that time. The reason for study termination was due to the inability to recruit enough patients within the time frame established.

Conclusions:

Due to the early study termination and limited data, the evolution of psoriasis disease severity over time after having discontinued long-term treatment with tildrakizumab could not be analysed; therefore, this study could not report any conclusion.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. DEMOGRAPHIC DATA

Attached separately.

14.2. EFFICACY DATA

Attached separately.

14.3. SAFETY DATA

Attached separately.

15. REFERENCE LIST

1. Feldman SR, Goffe B, Rice G, Mitchell M, Kaur M, Robertson D, et al. The Challenge of Managing Psoriasis: Unmet Medical Needs and Stakeholder Perspectives. Am Health Drug Benefits. 2016;9:504–13.

2. Pathirana D, Ormerod A, Saiag P, Smith C, Spuls P, Nast A, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol. 2009;23:1–70.

3. Blome C, Gosau R, Radtke MA, Reich K, Rustenbach SJ, Spehr C, et al. Patient-relevant treatment goals in psoriasis. Arch Dermatol Res. 2016;308:69–78.

4. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. J Am Acad Dermatol. 2008;58:826–50.

5. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. J Immunol Baltim Md 1950. 2018;201:1605–13.

6. Mrowietz U, Barker J, Boehncke W-H, Iversen L, Kirby B, Naldi L, et al. Clinical use of dimethyl fumarate in moderate-to-severe plaque-type psoriasis: a European expert consensus. J Eur Acad Dermatol Venereol. 2018;32:3–14.

7. Leczenie umiarkowanej i ciężkiej postaci łuszczycy plackowatej (Treatment of moderate to severe plaque psoriasis) [Internet]. Available from: https://www.gov.pl/web/zdrowie/choroby-nieonkologiczne

8. Puig L. The role of IL 23 in the treatment of psoriasis. Expert Rev Clin Immunol. 2017;13:525–34.

16. APPENDICES

16.1. STUDY INFORMATION

16.1.1	Protocol and Protocol Amendment	Included
16.1.2	Sample Case Report Form (unique pages only)	Included
16.1.3	List of IECs or IRBs (plus the name of the committee Chair if required by the competent authority) – Representative written information for patient and sample consent forms	Included
16.1.4	List and description of Investigators and other important participants in the study, including brief (1 page) curriculum vitae or equivalent summary of training and experience relevant to the performance of the clinical study	Included
16.1.5	Signatures of Principal Investigator or Sponsor's responsible medical officer	Included
16.1.6	Listing of patients receiving study drugs from specific batches, where more than one batch was used	Not applicable
16.1.7	Randomisation scheme and codes	Not applicable
16.1.8	Audit certificates	Included
16.1.9	Documentation of statistical methods	Included
16.1.10	Documentation of inter-laboratory standardisation methods and quality assurance procedures	Included
16.1.11	Publications based on the study	Not applicable
16.1.12	Important publications referenced in the report	Included

16.2. PATIENT DATA LISTINGS

16.2.1	Discontinued patients	Included
16.2.2	Protocol deviations	Included
16.2.3	Patients excluded from the efficacy analysis	Included
16.2.4	Demographic data	Included
16.2.5	Compliance and/or drug concentration data	Included
16.2.6	Individual efficacy response data	Included
16.2.7	Adverse event listings (each patient)	Included
16.2.8	Listing of individual laboratory measurements by patient	Included
16.2.9	Vital signs parameters	Included
16.2.10	Physical examination	Included

16.3. CASE REPORT FORMS

16.3.1	CRFs for deaths, other serious adverse events and withdrawals for adverse events	Not applicable
16.3.2	Other CRFs submitted	Not applicable

16.4. INDIVIDUAL SUBJECT DATA LISTINGS (US archival listings)

Not applicable.