Daratumumab as a treatment for adult immune thrombocytopenia (The DART Study)

A multicenter clinical, open label total dose-escalating with safety run-in

Investigational Medicinal Product: Daratumumab- Darzalex- L01FC01

Indication: adult patients with primary immune thrombocytopenia (ITP) who have not responded adequately or relapsed after corticosteroids and at least one second-line therapy, including rituximab or TPO-RA

Development phase of the study: phase II

Study initiation date: 21-January-2021

Study completion date: 12-March-2024

Sponsor: Sykehuset Østfold Kalnes

P.b. 300, 1714 Grålum

Coordinating Investigator: Waleed Ghanima, MD, PhD

The trial was conducted according to the International Council on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. The ethics committee of each participating institution approved the trial protocol.

Date: May 6, 2025

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)

OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Daratumumab as a treatment for adult immune thrombocytopenia (The DART study)

STUDY AUTHOR(S): Tsykunova, Ghanima et al.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR: Waleed Ghanima

DATE: May 6, 2025

Synopsis

Name of Sponsor/Company: Sykehuset Østfold Kalnes	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Darzalex	Volume:	
Name of Active Ingredient: Daratumumab	Page:	

Title of Study:
Daratumumab as a treatment for adult immune thrombocytopenia (The DART Study)

Investigators:
Norway: Waleed Ghanima, MD, PhD; Pål Andre Holme, MD, PhD; Hoa Thi Tuyet Tran, MD, PhD; Galina Tsykunova, MD
Denmark: Henrik Frederiksen, MD, PhD
France: Marc Michel, MD, PhD

Study centers:
Norway: Østfold Hospital Kalnes, Oslo University Hospital, Akershus University Hospital, Haukeland University Hospital
Denmark: Odense University Hospital
France: Henry Mondor University Hospital

Publication (reference):
Two publications were planned based on the results of the study:
1. Clinical aspects of daratumumab treatment: the article is submitted under the title " Safety and efficacy of daratumumab in immune thrombocytopenia."
2. Immunological aspects of daratumumab treatment: article under development

Studied period (years): 21 Jan 2021- 12 March 2024	Phase of development: phase II

OBJECTIVES

SAFETY RUN-IN:

Primary objective:
- to assess the safety and tolerability of daratumumab in patients with ITP
- other objectives as main study

MAIN PART:

Primary objective
- to determine the efficacy of treatment with daratumumab defined as response at week 12 for safety run-in and cohort 1, and week 16 for cohort 2
- to characterize the safety of daratumumab in patients with ITP.

Secondary objective
- to assess rates of sustained response (sR) at week 24
- to assess the duration of response (DOR)
- to determine the time to treatment failure (TTF)
- to assess bleeding complications during the study

EXPLORATORY OBJECTIVES:

- to characterize immunological effects of daratumumab treatment:
- to characterize various subsets of immunocompetent cells in the bone marrow and blood before, during daratumumab therapy and at study week 24 (only peripheral blood)
- to identify a potential biomarker (whether or not changes to antibody levels or levels of immunocompetent cells correlate with response)
- to determine HRQoL and level of fatigue before and after treatment with daratumumab and to assess

difference in HRQoL and fatigue between patients with or without response prior to and after daratumumab treatment
- to assess time from first dose of study medication to first platelet count ≥ 50 x109/L
- to assess rates of complete(CR) and partial(PR) response to daratumumab treatment

Methodology:
The first three patients were included in the safety run-in to evaluate worsening thrombocytopenia or any other severe life-threatening events attributable to the study drug. If no such events occur, consecutive patients in the first study cohort will receive 8 weekly doses of Daratumumab by subcutaneous route.
Rescue ITP medications (IVIG, steroids, anti-D, and platelet transfusions) are allowed during the first 8 weeks for safety run-in and cohort 1 and the first 12 weeks for cohort 2. The dose of steroids or TPO-RA (eltrombopag, romiplostim, or avatrombopag) must remain stable during the 2 weeks preceding the inclusion. Dose escalation is not allowed during the study.
If the initial response rate in cohort 1 is less than 100% without developing treatment-related SAE in >2 patients, the study will proceed with the second study cohort, where the patients will receive 8 weekly Daratumumab injections followed by 2 injections administered every other week. If the response rate is 100%, the subsequent 9 patients will receive the same number of daratumumab injections as cohort 1 (8 weekly injections)

Number of patients (planned and analyzed): 21 patients planned, included, and completed the study treatment and at least 24 weeks of observation.

Diagnosis and main criteria for inclusion:
Diagnosis: ITP
Main inclusion criteria:
Male or female aged ≥18 years with primary ITP with a platelet count of ≤30x10^9/L measured within 2 weeks prior to inclusion with failure to achieve response or relapse after corticosteroid therapy, and at least one second-line therapy including rituximab (last infusion ≥24weeks before study inclusion) and/or TPO-RA. The dose of steroids or/and TPO-RAs (romiplostim, eltrombopag, and avatrombopag) has not been changed during the last 2 weeks preceding the inclusion. A platelet count of 15-30x 10^9/L was required for the safety run-in phase.

Test product, dose and mode of administration, batch number:
Daratumumab1800 mg for subcutaneous administration

Duration of treatment:
Safety run-in: 4 weeks (4 weekly daratumumab injections, 1800 mg each)
Cohort 1: 8 weeks (8 weekly daratumumab injections, 1800 mg each)
Cohort 2: 12 weeks (8 weekly daratumumab injections followed by 2 bi-weekly injections, 1800 mg each)

Reference therapy, dose and mode of administration, batch number
N/A

Criteria for evaluation:
Efficacy:

The primary endpoint, response: proportion of patients who achieve platelet count ≥50x10^9/L in 2 measurements (taken at least 24 hours apart) during week 12 (safety run-in and Cohort 1) and week 16 (Cohort 2) after the first study drug injection, without having received rescue therapy for the last 4 weeks, nor having had dose increment of TPO-RA or corticosteroids during the study period.
Secondary endpoints:

- Sustained response (sR) defined as platelet count ≥ 50x10^9/L in 2 measurements (taken at least 24 hours apart) measured at study week 24 (+/- 2 weeks) without having received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids.
- Duration of response (DOR) defined as the duration of sustained platelet count ≥50x10^9/L without having received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids. Duration will not consider the 4 weeks following the last daratumumab injection in the study. Loss of response is defined as platelet count <50 x 10^9/L after achieving response in 2 consecutive blood samples taken at least 24 hours apart.
- Time to treatment failure (TTF) defined as the time with platelet count ≥50x10^9/L from 4 weeks after the last daratumumab injection to the first platelet count <30x10^9/L of two counts taken in two consecutive measurements

at least 24 hours apart or administration of any platelet elevating therapy after achieving response. Date of the first platelet count measurement or administration of platelet elevation therapy will be used to calculate TTF.

- -Total number of bleeding episodes per patient; maximum severity on the World Health Organization (WHO) bleeding scale; change in Khellaf score measured on the day of first daratumumab administration and at study week 24.

Safety: incidence, severity, and relationship of treatment-emergent adverse events

Statistical methods: Data were analyzed for all enrolled patients. Baseline characteristics are presented using descriptive statistics. The 95% confidence intervals (CI) for the evaluation of primary and secondary endpoints were calculated using the Clopper-Pearson method. Time-to-event estimates were evaluated using the Kaplan-Meier method. No replacement of missing data was performed. No formal hypothesis was planned in this study as the statistical power was insufficient to detect differences between dose groups.

Summary - Conclusions

Efficacy Results:

The primary endpoint, response, was met in 10 patients (48%), 95% CI 25.7-70.2), with one additional patient responding at week 14, and an overall response rate of 52%.

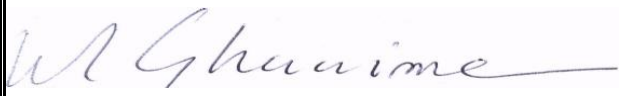
Sustained response was achieved in 8 patients (38%, 95% CI 18.1-61.6). The median duration of response was 653 days (range, 35-1010), time to treatment failure was 680 days (range, 35-1010). Seven patients experienced bleeding episodes during the study period; all were WHO grade 2, and none were related to treatment.

Safety Results:

During the study period, 43% experienced at least 1 treatment-related adverse event (TRAE), all transient. The most common TRAEs were infusion-related reactions, IRR (14%), injection site reactions (9.5%), and diarrhea (9.5%). Infections were the most common treatment-emergent adverse events (38%). In total, 3 adverse events of grade 3 occurred in 2 patients. One was an IRR. The second was SARS-CoV-2 infection complicated by acute renal failure. No grade 4 adverse events were observed.

Conclusion

Treatment with daratumumab in ITP patients shows promising results with an acceptable safety profile.



Date of report May,6 2025

Innholdsfortegnelse

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event

AESI	Adverse events of special interest
CI	Confidence interval
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
HRQoL	Health Related Quality of Life
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRR	Infusion-related reactions
ITP	Immune thrombocytopenic purpura
IVIG	Intravenous immunoglobuline
SAE	Serious adverse event
SUSAR	Syspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse events
TPO-RA	Thrombopoietin-receptor agonist
TRAE	Treatment-related adverse events
WHO	World Health Organization

1. Ethics

1.1 Independent Ethics Committee (IEC)

The study was approved by Independent Ethics Committees in all participating countries and participating institutions. A detailed overview is provided in Appendix 12.1

1.2 Ethical Conduct of the Study

The trial was conducted according to the International Council on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

1.3 Patient Information and Consent

All patients provided written informed consent before trial entry.

2. Investigators study administrative structure

DART was an investigator-initiated trial sponsored by Østfold Hospital in Norway and financed through a grant from the South-East Norwegian Health Region. The investigational trial product was provided free of charge by Janssen. The coordinating investigator coordinated all sites participating in this multicenter trial. The principal investigators of each site were responsible for ensuring proper conduct of the study, patient care, and safety.
Blood and bone marrow samples were sent to Rikshospitalet (Department of Immunology and Transfusion Medicine, Section for Cellular Immunology, Sognvannsveien 20, 0372 Oslo) for cell separation and subsequent flow cytometry and mass cytometry analysis.
Blood for antibody determination was sent to Tromsø for analysis (Laboratoriemedisin v/ Trombocyttlaboratoriet, Sykehusvegen 38, 9038 Tromsø).
A steering committee, including the coordinating investigator, a selected number of investigators participating in the trial, or other experts, monitored the study regularly. An independent committee (DSMB) was constituted for the trial and was responsible for blindly reviewing the efficacy and safety data of the center.

An independent medical monitor accessed all SAE and AESI.

Principal investigators oversee the trial at each hospital.
A detailed overview of investigators and study administrative structure is given in Appendix 12.2

3. Introduction

Immune thrombocytopenia (ITP) is an acquired bleeding disorder characterized by immune-mediated destruction of platelets and megakaryocytes. It is defined as isolated thrombocytopenia with platelet count <100 X 10^9/L and no identifiable underlying cause.[1] The pathogenesis of ITP remains unclear, although both antibody-mediated and/or T cell-mediated platelet destruction are key processes. In addition, impairment of T cells, cytokine imbalances, and the contribution of the bone marrow niche have now been recognized to be important.[2]

ITP has an annual incidence of 2 to 6 per 100,000 in adults.[3,4] Since ITP usually is a chronic disorder, the prevalence is much higher than the incidence and is estimated to be between 8 and 25 per 100,000 individuals.[5,6]

The main goal in the therapy of acute ITP is to achieve sustained, hemostatic platelet counts to prevent bleeding. Generally, a platelet count below 20-30 x10^9/L is used as a threshold for treatment.[7] Glucocorticoids are the first-line treatment choice, but few patients achieve long-term remissions. Consequently, the majority of ITP patients require second-line therapies, including TPO-RAs, rituximab, or immunomodulatory agents.[7] Although many patients respond to the second-line therapies, many relapse after the initial response. Rituximab, a B cell-depleting anti-CD20 antibody, has been used for years to treat ITP. Despite an initial response of 60%, many patients relapse within a few years.[8,9] The reason for that is not well understood but may include mechanisms such as persistence of CD20-memory B-cells and the emergence of long-lived plasma cells.[10–12]

Daratumumab, which targets CD38 expressed on several immune cells, including long-lived plasma cells, has been extensively used in multiple myeloma and has a well-established safety profile. Beyond plasma cells and plasmablasts, daratumumab targets other CD38-expressing cells, including subsets of B and T cells, dendritic cells, and NK cells.[13]

Single case reports, and small case series suggested that anti-CD38 antibody daratumumab has activity in autoimmune diseases, including ITP.[14–16]

Our hypothesis for this study was based on the evidence that lack of response to/multi-drug refractoriness is related to the emergence/presence of antibody-producing. These long-lived plasma cells maintain the autoimmune process. Therefore, anti-CD38 may eliminate the autoantibody-secreting long-lived plasma cells and consequently induce response in these patients.

4. Study Objectives

SAFETY RUN-IN:

Primary objective:

- to assess safety and tolerability of daratumumab in patients with ITP
- other objectives as main study

MAIN PART:

Primary objective

- to determine the efficacy of treatment with daratumumab defined as response at week 12 for safety run-in and cohort 1, and week 16 for cohort 2
- to characterize the safety of daratumumab in patients with ITP.

Secondary objective

- to assess rates of sustained response (sR) at week 24
- to assess the duration of response (DOR)
- to determine the time to treatment failure (TTF)
- to assess bleeding complications during the study

EXPLORATORY OBJECTIVES:

- to characterize immunological effects of daratumumab treatment:
- to characterize various subsets of immunocompetent cells in the bone marrow and blood before, during daratumumab therapy and at study week 24 (only peripheral blood)
- to identify a potential biomarker (whether or not changes to antibody levels or levels of immunocompetent cells correlate with response)

- to determine HRQoL and level of fatigue before and after treatment with daratumumab and to assess difference in HRQoL and fatigue between patients with or without response prior to and after daratumumab treatment
- to assess time from first dose of study medication to first platelet count $\geq$ 50 x109/L
- to assess rates of complete (CR) and partial (PR) response to daratumumab treatment

5. Investigational Plan

5.1 Overall Study Design and Plan Description

The study was designed as a multicenter clinical, open label phase II study with a safety run-in.

A total of 21 patients were included. The first 3 patients were recruited to the safety run-in and treated with a standard subcutaneous dose of 1800 mg Daratumumab once weekly for four subsequent weeks. During the safety run-in, no more than only one patient was included at a time. The decision to enroll the next patient in the safety run-in phase was made after a careful assessment of safety aspects by Data Safety and Monitoring Board members in collaboration with the principal investigator in each site and only after the communication with and the personal approval by the coordinating investigator.

The remaining 18 patients were recruited to one of two consecutive cohorts of 9 patients each to receive either 8 or 12 weeks of treatment with daratumumab.

Inclusion to cohort 1 started only after the evaluation and written approval of safety aspects in the safety run-in group by members of DSMB. Likewise, inclusion to cohort 2 began only after the evaluation and written approval of safety aspects in the safety run-in group and cohort 1 by members of DSMB.

Only patients in cohort 2 were included by French centers after the evaluation and written approval of safety aspects in the safety run-in group and cohort 1 by the members of DSMB.

The study scheme is provided in Fig.1

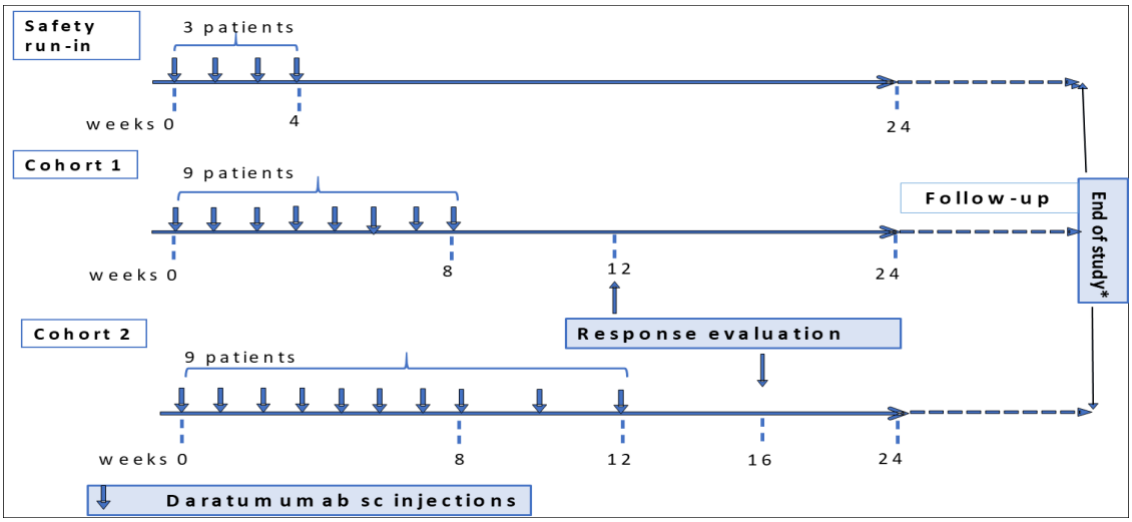

Figure 1. Study scheme. * Last visit (at week 24) for the last patient.

5.2 Discussion of Study Design

We have chosen a multicenter clinical, open label total dose-escalating phase II study with a safety run-in – a design used in dose-finding, safety, and toxicity studies.[17,18] This is because 1-we did not have safety data of daratumumab in ITP; 2-we did not know whether the treatment was effective or not, and if effective, the effect size of this treatment; 3-we did not know the dose required to induce effect; 4-to adopt a vigilant approach to avoid toxicity.

No formal hypothesis was tested in this study.

Since daratumumab can cause thrombocytopenia, the first three patients were included in the safety run-in evaluation. These three patients received one cycle of four weekly injections only. If no severe worsening in thrombocytopenia was encountered after the administration of the first cycle or any other severe life-threatening event occurred during the safety run-in, we would proceed to the main part of the study.

We opted for 9 patients per cohort and a total of 21 patients in the study, which is an acceptable number of patients used in dose-finding/safety studies. We believed that this design allowed us to explore the total dose needed to induce effect as well as to determine the safety of this medication in ITP.[19]

Following the four daratumumab injections in a safety run-in, patients with the response and those with the partial response not requiring other ITP-directed therapy were followed up until the end of the study to explore long-term safety and efficacy. Patients with no response were followed until study week 24.

The subsequent 9 patients received 8 weekly injections each. As the response rate at week 12 was less than 100% and no serious safety concerns were raised, we proceeded with the next

cohort, where 9 patients received 8 weekly injections followed by 2 injections every other week (biweekly).

We did not believe that escalation beyond 12 weeks of treatment would increase the response rate. The findings of a recent study substantiate this.[20]

However, quantifying the plasma cells by immunophenotyping after treatment would determine if the plasma cells were eradicated entirely or not. Incomplete eradication of the plasma cells would justify additional treatments in further studies.

This study required a significant time interval from previous treatment to reduce the risk of late treatment effects from previous treatment. The study population included ITP patients with failure to achieve response or relapse after corticosteroid therapy and at least one second-line therapy, including rituximab ≥24 weeks ago or TPO-RA. Patients were allowed to receive other platelet-elevating therapies (steroids and I.V. immunoglobulin) during the treatment in case of severe thrombocytopenia or bleeding. Administration of any platelet elevating therapy after completion of the study treatment period qualified the patient as a non-responder. The dose of steroids and/or TPO-RA (eltrombopag, romiplostim, or avatrombopag) had to remain stable during the 2 weeks preceding the inclusion. Dose escalation is prohibited during the study and will qualify as a treatment failure.

Evaluation of the primary efficacy endpoint and response was set at 4 weeks after administering the last dose of study treatment. This was to eliminate a possible effect of glucocorticoids, used as premedication, on platelet count elevation.

Hence, a significant increase in platelet count in the study population could be attributed to the study drug.

RATIONALE FOR ELIGIBILITY CRITERIA

We required that patients eligible for this study had previously been treated with rituximab and/or TPO-RA. Although current literature indicates the emergence of plasma cells in patients treated with rituximab, a substantial number of patients do not respond to rituximab and/or other treatments, possibly because of the existence of autoreactive plasma cells prior to treatment with rituximab. Thus, these patients may theoretically also respond to daratumumab.

RATIONALE STUDY ENDPOINTS

Elevation of platelet count is a standard endpoint used for efficacy in ITP studies. We used a platelet count of $\geq 50x10^9$/L to define response as frequently used in clinical studies. The primary efficacy endpoint, response (at 12 weeks for safety run-in and cohort 1, and 16 weeks for cohort 2), and the secondary endpoint, sustained response (at 24 weeks for all patients), accessed both the number /proportion of patients who achieve platelet count $\geq 50x10^9$/L and the duration of response.

In addition, frequent platelet counts and extended follow-up until the end of the study were aimed to capture changes in platelet count during the follow-up period. We followed all responding and non-responding patients who did not require additional ITP-directed therapies until the end of the study (the last visit for the last patient) to further evaluate the potential of daratumumab to induce long-term remissions in responding patients.

Bleeding was assessed using WHO grading system for bleeding and Khellaf bleeding score.

Although the safety of daratumumab is well-characterized for multiple myeloma, its safety is unknown in ITP. As such, the safety aspects evaluation of daratumumab treatment in ITP patient population was one of two main aspects of this study.

5.3 Selection of Study Population

5.3.1 ***Inclusion criteria***

1. Male or female aged ≥18 years.
2. Primary ITP with a platelet count of $<30x10^9$/L measured within 2 weeks prior to inclusion with failure to achieve response or relapse after corticosteroid therapy and at least one second-line therapy including rituximab (last infusion≥ 24 weeks before) and/or TPO-RA. The dose of steroids or/and TPO-RAs (romiplostim, eltrombopag, and avatrombopag) has not been changed during the last 2 weeks preceding the inclusion. A platelet count of 15-30x 10^9/L will be required for the safety run-in phase.
3. Signed and dated written informed consent.
4. Females of childbearing potential accepting to follow effective contraceptive methods for at least 24 weeks following the administration of the first daratumumab injection. A man who has not had a vasectomy and who is sexually active with a woman of childbearing potential must agree to use a barrier method of birth control, e.g., condom with spermicidal foam/film/gel/cream/ suppository, and all men must also not donate sperm during the study and for 3 month following discontinuation of Daratumumab.

Criteria for enrollment to safety run-in:

- all inclusion criteria should be met
- none of exclusion criteria should be met
- a platelet counts of 15-30x 10^9/L measured within 2 weeks before the inclusion.
- previous steroid and/ or IVIG responsive disease with platelet count $\geq$50x10^9/L after steroid and/or IVIG treatment.

5.3.2 *Exclusion Criteria*

1. Patients with active bleeding during the last 7 days prior to inclusion. Active bleeding is defined as any clinically overt hemorrhage (including radiologically diagnosed bleeding) with ongoing hemoglobin fall or bleeding requiring immediate intervention.
2. Pregnancy or lactation.
3. Surgery planned within the 3 next months.
4. Secondary ITP: ITP associated with lymphoma, chronic lymphocytic leukemia, drug-induced or ITP secondary to autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, common variable immune deficiency, human immunodeficiency virus, or hepatitis C.
5. Concomitant autoimmune hemolytic anemia.
6. Known allergy and/or sensitivity or contraindication to daratumumab.
7. Current active malignancy likely to require chemo-or surgical treatment during the study period or within one year after the start of the study treatment
8. Patients with history of poor compliance or history of alcohol/drug abuse or excessive alcohol beverage consumption that would interfere with the ability to comply with the study protocol, or current or past psychiatric disease that might interfere with the ability to comply with the study protocol or give informed consent.
9. Patient unable to attend all the visits planned for the trial.
10. Positive at screening for Hepatitis B virus (HBV)(surface and core antibodies unrelated to vaccination):
    - Patients with positive HBV surface antigen (HBsAg) are not eligible.
    - Patients who are HBsAg negative and HBV core antigen antibody positive (HBcAb) will be tested for HBV surface antibody (HBsAb) and HBV DNA. If HBsAb titer is >100 IU/ml, patients may be enrolled. Monthly HBV DNA monitoring will be required while on treatment and for the 6 months after the

last dose of the study drug

- Patients who are HBcAb positive, HBsAg negative with HBsAb titer <100 IU/ml or negative, are not eligible

11. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note that forced expiratory volume at one second FEV1 testing is required for participants suspected of having COPD
12. Known moderate or severe persistent asthma within the past 2 years, uncontrolled asthma of any classification.
13. Patient participating in another clinical trial with an investigational drug.

5.3.3 Removal of patients from therapy and assessment

Premature study drug discontinuation

The study treatment should be permanently discontinued under the following circumstances:

1. Life-threatening allergic reaction to daratumumab.
2. Related AEs: study treatment can be stopped following a severe or life-threatening adverse experience at the discretion of the treating investigator and after a thorough discussion with the study team.
3. Non-related AEs: study treatment can be stopped/delayed following a severe or life-threatening adverse experience, at the discretion of the treating investigator. Study treatment can be resumed to reach the planned number of study drug treatments after the resolution of adverse event at the discretion of the treating investigator and after the thorough discussion with the study team.
4. In the case of irrevocable decision by the patient and/or the responsible investigator patients will be asked for giving their authorization to undergo the scheduled study follow-up, as treatment refusal does not imply a complete study discontinuation.
5. Special precautions for the safety run-in phase: study treatment should be discontinued in case of severe worsening of thrombocytopenia emerges in >1 patient, where severe thrombocytopenia is defined as fall in platelet count $\leq 5x10^9$/l that persists for > 5 days and is refractory to standard rescue therapy or causes major bleeding or any other severe life treating AE occur

The decision to discontinue study medication for any reason must always be discussed and made in collaboration with the study team.

Discontinuation of study treatment is not considered as study discontinuation or premature withdrawal.

Patient withdrawal

A patient may voluntarily withdraw his or her consent for the participation in this study at any time:

- If a patient is prematurely discontinued from the study for any reason, before the first study drug administration, the investigator must complete the End of Study form.
- If a patient is prematurely discontinued from the study for any reason, after the first study drug administration, the investigator must make every effort to perform the assessments as outlined in the End of Study evaluation. These data should be recorded in the medical record and eCRF, as they represent an essential evaluation that should be done prior to discharging any patient from the study.

The primary reason for withdrawal will be clearly documented in the patient's medical record and recorded in the eCRF. If a patient has a premature treatment discontinuation, he/she should stay in the study, as far as possible (see section 12.3).

Pregnancy and lactation

Should a pregnancy occur, the study participant must immediately inform the investigator and must immediately discontinue the study drug. Given the subject's participation in the study, the investigator should counsel the study participant on any risks of continuing the pregnancy and any possible effects on the fetus. The study participant must agree to follow up with the investigator regarding the outcome of any pregnancy during the study. Outcome is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed by the investigator until 30 days old. Any congenital abnormality/ birth defect noted in the infant must be reported as an SAE.

5.4 Treatments

5.4.1 Treatments administered

Daratumumab 1800 mg (flat dose) in combination with recombinant human hyaluronidase PH20 (rHuPH20) 2000 Units/mL subcutaneous injections was administered by manual push

(15 mL) over 3-5 min at alternating left/right abdominal sites weekly for 8 weeks in cohort 1, and weekly for 8 weeks followed by 2 injections given every other week (biweekly) at week 10 and 12 for cohort 2.

5.4.2 Identity of investigational product

Daratumumab 1800 mg with rHuPH20 30,000 Units for subcutaneous administration
Janssen provided Daratumumab to each site. Daratumumab was shipped to clinical supplies management (CSM), where it was labeled, released, and distributed to the sites. The sponsor contracted these activities since they are the sponsor`s responsibility.
Daratumumab was stored in a refrigerator at the local pharmacy in the original carton at controlled temperatures ranging from 2° to 8°C until it was removed for administration. Daratumumab could not be utilized after the expiry date printed on the label. Daratumumab must be protected from light and must not be frozen. The product did not contain preservatives, therefore, any unused portion remaining in the vial was discarded.
Batch numbers are provided in Appendix12.3

5.4.3 Method of assigning patients to treatment group

This study consisted of 3 consecutive phases: safety run-in, cohort 1, and cohort 2.
Safety run-in phase of the study: 3 patients received 4 weeks of study treatment followed by a 4-week observation period. Enrollment of the next patient in this phase occurred only after the previous patient completed treatment and the observation period. The decision to enroll the next patient in the safety run-in phase will be made after a careful assessment of safety aspects by Data Safety and Monitoring Board members in collaboration with the principal investigator in each site and only after the communication with and the personal approval by the coordinating investigator.
In the subsequent study phase, 9 patients (cohort 1) received 8 weeks of study treatment; in cohort 2, 9 subsequent patients received 12 weeks of study treatment.
Inclusion to cohort 1 could start only after the evaluation and written approval of safety aspects in the safety run-in group by members of DSMB. Likewise, inclusion to cohort 2 could begin only after the evaluation and written approval of safety aspects in the safety run-in group and cohort 1 by members of DSMB.
If the initial response rate in cohort 1 were less than 100% without the development of treatment-related SAE in >2 patients, we would proceed with the second study cohort, where

the patients would receive 8 weekly Daratumumab injections followed by 2 injections administered every other week (12 weeks of study treatment). If the response rate were 100%, the subsequent 9 patients would receive the same number of daratumumab injections as cohort 1 (8 weekly injections) (Appendix 12.4).

5.4.4 Selection of doses in the study

All patients received IMP daratumumab at a flat dose of 1800 mg administered subcutaneously.

We used the same dose of daratumumab used in multiple myeloma involving subcutaneous injections of 1800 mg administered weekly. Subcutaneous administration is the preferred mode of administration because of the ease of administration and the lower rate of infusion-related reactions with subcutaneous administration compared to intravenous route.[21]

5.4.5 Selection and timing of dose for each patient.

We used the same schedule of daratumumab used in multiple myeloma, but we chose a definite number of injections.[21]

It is possible that ITP patients require much shorter treatment (lower total dose) than those with multiple myeloma since the plasma cell load is much lower in ITP than in multiple myeloma. Therefore, the first cohort received 8 weekly injections, whereas the second cohort received 2 additional injections in weeks 10 and 12.

5.4.6 Randomization and blinding

All patients in the study are included either to safety run-in, cohort 1 or cohort 2. The inclusion of different cohorts takes place based on the order of inclusion. No randomization was conducted in this study. All patients received open-label study treatment. As such, no blinding will be performed in this study.

5.4.7 Concomitant therapy

Concomitant medication and rescue therapy

All treatments given in addition to the study treatments (including any premedication before study drug administration and any ITP treatments) after inclusion in the trial were concomitant treatments and must be documented in the appropriate form of the eCRF.

Concomitant therapy

Steroids and TPO-Ras were allowed during the study. Dose increment was not allowed during the study.

Any change in the dose of steroids or/and TPO-RAs (romiplostim, eltrombopag, or avatrombopag) in the 2 weeks preceding the inclusion would prevent the inclusion in the study.

It was recommended that all patients receive prophylaxis against varicella zoster virus reactivation with Valacyclovir 250-500 mg twice a day (or as per institutional standards), which must be initiated within one week after the initiation of daratumumab therapy and continued within 3 months after the last daratumumab injection.

Rescue therapy

Platelet transfusion and/or intravenous immunoglobulin (IVIG) (1g/kg daily for 2 consecutive days, or 0.4 g/kg daily for 5 consecutive days) with or without platelet concentrates, i.v. Methylprednisolone (1000 mg) were considered rescue therapies and can be given in case of severe thrombocytopenia and/or bleeding. Rescue therapies were allowed until the day of the administration of the last injection of study treatment. Treatment with rescue medications after that qualified patients as patients with no response or treatment failure, except if the rescue medication was given preoperatively to elevate platelet counts > $50x10^9$/L.

All the following platelet-elevating therapies were prohibited during the study:

- Chemotherapy (vincristine or cyclophosphamide);
- Anti-CD20 preparations
- Immunosuppressive agents.
- Dapsone or Danazol.
- Splenectomy.

Administration or application of any of these prohibited therapies at any time after inclusion in the study qualified the patient as patients with no response or loss of overall response unless the rescue therapy was for an indication other than ITP. Such patients would be regarded as having a treatment failure and withdrawn from the study treatment.

Notably, all patients reaching the study endpoint were allowed to receive any treatment for ITP.

5.4.8 Treatment compliance

Accurate study intervention administration (daratumumab) recording was made in the appropriate section of the participant's case report form (eCRF) and source documents. The investigator or designee is responsible for accounting for all study-specific treatment either administered or in their custody during the course of the study.

5.5 Efficacy and Safety Variables

5.5.1 Efficacy and safety measurements assessments

- The Schedule of Activities (Appendix 12.5) summarizes study procedures and timing.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record all participants' details and confirm eligibility or record reasons for screening failure, as applicable.
- Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

5.5.2 Primary efficacy variables

The primary efficacy of treatment with daratumumab was defined as response at week 12 for safety run-in and cohort 1 and week 16 for cohort 2.

Response was defined as:

- Safety run-in and cohort 1: proportion of patients who achieve platelet count $\geq 50 \times 10^9$/L in 2 measurements (taken at least 24 hours apart) during week 12 (after first study drug injection), without having received rescue therapy for the last 4 weeks, nor having had dose increment of TPO-RA or corticosteroids during the study period
- Cohort 2: proportion of patients who achieve platelet count $\geq 50 \times 10^9$/L in 2 measurements (taken at least 24 hours apart) during week 16 after first study drug injection without having received rescue therapy for the last 4 weeks, nor having had

dose increment of TPO-RA or corticosteroids during the study period

5.5.3 Immunogenicity assessment

Blood samples (5 mL) were collected in plasma from all participants (only Norwegian study centers) to measure ADA against daratumumab. Blood samples were taken at weeks 1,4,8,12, 24 at safety run-in and cohort 1 and at weeks 1,4,8,16,24 at cohort 2. Blood tests at week 24 were taken from all patients but analyzed only in case of positive samples at week 12 (or 16 for cohort 2) for each patient. If no ADA against daratumumab were detected in the safety run-in and cohort 1, then ADA analysis in cohort 2 could be entirely omitted.
Plasma samples were screened for antibodies binding to daratumumab, and the titer of confirmed positive samples would be reported. Positive samples would also be tested for the neutralizing effect against daratumumab. All remaining samples would be destroyed after the statistical analysis results have been regarded as final by the study coordinator and the members of DSMB.

5.5.4 Platelet antibodies analyses (only Norwegian centers).

Anti-GPIIb/IIIa and Ib measured by direct MAIPA test before daratumumab therapy, week 4 (safety run-in),week 12 (cohort 1), week 16 (cohort 2) and at study week 24 for all included paeents. Further we include selected samples to analyze autoantibodies to the proteome, in beads-based array with 12 000 autoantigens for flow cytometry analysis.

5.5.5 Study specific analyses (only Norwegian and French centers)

Blood samples for study specific analyses are taken week 4 (all patients), 12 (safety run-in and cohort 1), 16 (cohort 2), and 24 (all patients)
Bone marrow samples will be taken at week 0 and 12 for safety run-in and cohort 1 and week 0 and 16 for cohort 2.

5.5.6 Health-related quality of life and fatigue.

Measurement of HRQoL and fatigue using SF36v1 and MFI-20 questionnaire before daratumumab therapy, at week 8 for safety run-in, at week 12 for cohort 1, at week 16 for cohort 2 and at study week 24 for all patients in the study

5.6 Data Quality Assurance

Source Data and Documents

Source data are all information available in the original source document or certified copies of the source document of any clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study.

For each patient included, the investigator indicates in the source documents that the patient participates in this study and will record the appropriate information, including (non-exhaustive list): patient's name, date of birth, sex, medical history, visit dates, product administration, primary evaluation criteria, nature of AEs with date of start and related treatment.

The investigator permit study-related monitoring, audit(s), and regulatory inspection(s), with direct access to any required source documents when necessary, provided that the confidentiality of the patient's data is protected. The extent of source data verification performed by the Clinical Research Assistant is 100% of critical data (regarding eligibility criteria, treatment administration, safety, and efficacy assessment) to be verified per eCRF. Source documents will be preserved for the maximum period of time requested by local recommendations or ICH, whichever occurs the last.

Periodic Monitoring

In addition to the initial visit for site set-up, the Clinical Research Organization (CRO) contacted and visited periodically the investigator to evaluate the study progress and the compliance of the investigational site. Study monitors performed an ongoing source data verification according to standard operating procedure to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents; that the safety and rights of participants were protected; and that the study was conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Site initiation visit could only find place when the relevant authorities have approved all necessary regulatory formalities, and all relevant legal documents have been signed

Globally, the first on-site monitoring visit was performed per included patient. Site visits to each center were performed roughly every 6 months during the treatment period and every 12 months during the follow-up period.

For-cause monitoring visits were allowed, as deemed necessary, with the sponsor's and coordinating investigator's approval. Those monitoring visits could be requested in the following cases:

- recruitment rate (lower or higher than expected)
- eCRF issues (low entry volume, many missing data, high number of queries)
- study non-compliance (recurrent protocol deviations/major issues identified)
- suspicion of fraud
- significant change in study stuff.

In addition to on-site monitoring, remote monitoring by phone were performed:

- as quality control for missing data
- to validate data entered by the site staff in the electronic database (eCRF)
- regularly: (every 6 months during the inclusion period) and 1 per year during the follow-up period. The frequency of remote monitoring could be adapted upon CRA request, depending on the site recruitment rate and after validation by coordinating investigator

The study was monitored risk-based, and the procedures are described in detail in the "Study Monitoring Plan."
The sponsor monitored the trial in Norway with the help of CRO -Regional Forskningsstøtte at Oslo University Hospital. In Denmark, the trial will be monitored by GCP-Enheden at Odense University Hospital. The CRO Monitoring Force Group will monitor the trial in France.

5.7 Sample size and statistical analysis

No formal statistical hypothesis was tested in this study. In total, 21 patients were included in the study. The first three patients were included in a safety run-in phase, and nine were included in each subsequent cohort. Baseline characteristics of all patients and patients in the two treatment cohorts are summarized by numbers and proportion and mean/median with corresponding standard deviation/interquartile range, depending on the normality distribution of the parameter.
The primary outcome, response at weeks 12 and 16 after the first study drug administration for safety run-in, cohorts 1 and 2, respectively, and at week 24 for both cohorts, is expressed

by absolute numbers and rates with the corresponding two-sided 95% confidence interval. In addition, we report the total response rate in the whole population, including the run-in cohort. The study medication was to be considered as successful if minimum response rate of 30% was achieved.

The 95% confidence intervals (CI) for evaluation of primary and secondary endpoints were calculated using the Clopper-Pearson method. Time-to-event estimates were evaluated using the Kaplan-Meier method. Median and interquartile range times of duration of response were estimated on the subpopulation of patients with initial response using Kaplan-Meier method. Kaplan Meier curve are displayed. No replacement of missing data was performed.

Patients with a response are censored at death, date of last news, or end of study, which event occurs first.

Adverse events (all and grade >2), SAE, and SUSARs are presented in numbers and proportions. Other secondary outcomes, including the number and proportion of patients who have achieved a complete response and the rate of bleeding episodes stratified by the grade, according to WHO classification, will be reported by absolute numbers and percentages. Khellaf bleeding score will be summarized as a continuous parameter.

Analysis was performed using a modified intention-to-treat approach, which requires the administration of at least one study drug injection.

Changes in individual domains and summary scores of SF-36 and MF1-20 are presented in figures and numbers. A detailed statistical analytic plan was developed before the end of the study to describe the analysis in detail.

5.8 Changes in the Conduct of the Study or Planned Analyses

No changes were made to the study or planned analyses.

6. Study Patients

6.1 Disposition of Patients

Twenty-one patients were screened and enrolled in the study. All enrolled patients completed study treatment and were followed until week 24. Eleven patients discontinued treatment at study week 24. Ten patients continued study treatment until either the end of the study (last

visit for the last patient), relapse, or indication for any other ITP-directed therapy(Fig.2). No patients discontinued study treatment.

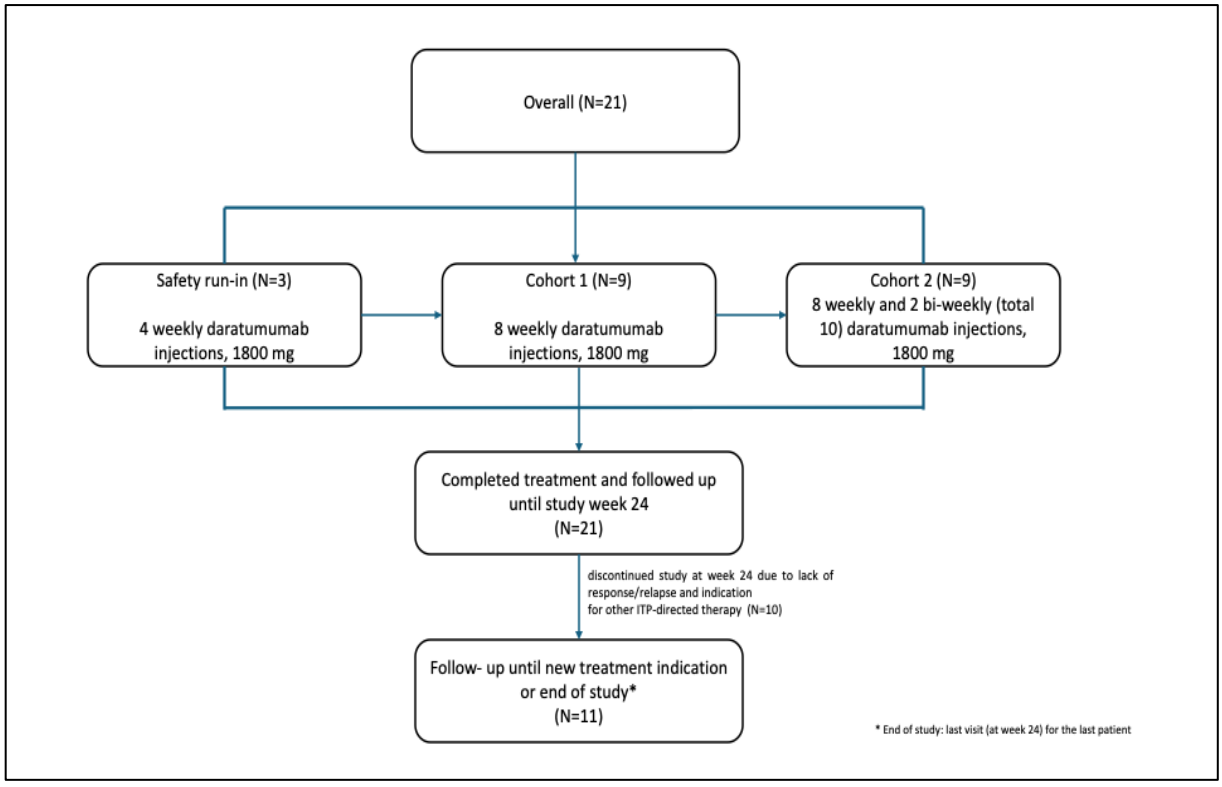

Fig. 2 Consort diagram of the study

6.2 Protocol Deviations

In total, 10 protocol deviations were reported

Two deviations were considered important.

One patient entered the study even though one exclusion criterium for entry was fulfilled. The patient had a positive hepatitis B core antibody and hepatitis B surface antibody but negative Hepatitis B surface antigen, with values declining over time. The patient denied previous hepatitis B infection, and did not remember having been vaccinated against Hepatitis B.

The patient had recently received IVIG, and use of IVIG which could cross react with hepatitis test results, was considered to be the most likely explanation.

Decision to include the patient was done after the thorough discussion with infectious disease specialist, and in agreement with all members of Steering Committee. The patient did not have any other available treatment alternatives for ITP.

After agreement with infectious disease specialist, the patient received entecavir prophylaxis.

The second patient forgot to take antiviral prophylaxis for 2 weeks following last IMP injection. The prophylaxis was resumed after 2 weeks.

Protocol deviations are summarized in Appendix 12.6.

7. Efficacy Evaluation

7.1 Data Sets Analysed

Definition of population for analysis

- INTENT TO TREAT (ITT) includes all enrolled subjects.
- FULL ANALYSIS SET (FAS) includes all enrolled subjects who received at least one dose of the study treatment and had at least one valid platelet count after treatment. If the subject was included and no study drug treatment has been received, then he/ she will be excluded from the FAS as actual treatment is missing. Subject will be analyzed according to cohort and as a whole group.
- PER PROTOCOL (PP) includes all patients in the FAS and with no major protocol violations
- IMMUNOGENECITY SET (IMGS) includes all patients who receive at least one dose of the study drug and have at least one valid immunogenicity data amer the first study drug administraeon
- SAFETY SET (SS) includes all patients who received one dose or more of the study drug.

Efficacy data was analyzed for all 21 enrolled patients as all patients received at least one dose with IMP.

7.2 Demographic and Other baseline Characteristics

Overview over demographic characteristics, disease factors and other relevant factors is presented in Table 1.

Table 1. Patient characteristics

Characteristics	**All patients (N=21)**	**Safety run-in (N=3)**	**Cohort 1 (N=9)**	**Cohort 2 (N=9)**
Median age (IQR)-yr	51 (34-65)	55 (33-75)	51 (36-67)	49 (33-59)
Sex- no.(%) Male Female	 14 (66.7) 7 (33.3)	 2 (66.7) 1 (33.3)	 5 (55.6) 4 (44.4)	 7 (77.8) 2 (22.2)
Median BMI (IQR)- kg/m^2	29.3 (26.0-33.3)	35.0 (28.0-42.2)	29·4 (26.0-32.2)	28·7 (25.3-33.3)
Median platelets count at screening (IQR)- 10^9/L	17.0 (10.0-20.0)	17.0 (16.0-26.0)	19.0 (15.0-22.0)	16.0 (10.0-19.0)
Median duration of ITP* (IQR)-months	60.5 (13.5- 231.7)	108.8 (13.5-136.8)	18.3 (7.3-60.5)	231.4 (42.0- 272.9)

Median number of different prior ITP treatments (range)	4 (2-11)	5 (3-6)	4 (2-9)	4 (3-11)
Prior ITP therapy- no.(%)				
Corticosteroids	21 (100)	3 (100)	9 (100)	9 (100)
IVIG	14 (67)	2 (67)	5 (56)	7 (78)
Rituximab	16 (76)	3 (100)	6 (67)	7 (78)
Thrombopoietin-receptor agonists†	18 (86)	3 (100)	8 (67)	7 (78)
Fostamatinib	1 (4.8)	0	0	1 (11)
Rilzabrutinib	1 (5)	1 (33)	0	0
Azathioprine	2 (10)	0	1 (11)	1 (11)
Mycophenolate mofetil	2 (10)	0	0	2 (22)
Dapsone	1 (5)	0	0	1 (11)
Danazol	1 (5)	0	1 (11)	0
Cyclosporine	2 (10)	0	0	2 (22)
Hydroxychloroquine	1 (4.8)	0	0	1 (11)
Splenectomy	5 (24)	0	2 (22)	3 (33)
Concomitant ITP directed therapy (at the date of the first daratumumab injection)-no.(%)				
Corticosteroids monotherapy	3 (14)	0	0	3 (33)
Thrombopoietin receptor agonists monotherapy	5 (24)	1 (33)	2 (22)	2 (22)
Thrombopoietin-receptor agonists and corticosteroids combined	5 (24)	2 (67)	1 (11)	2 (22)

* The duration of ITP was defined as a time from date of ITP diagnosis to the date of baseline evaluation
† Thrombopoietin-receptor agonists include eltrombopag, avatrombopag and romiplostim
ITP, immune thrombocytopenic purpura
BMI, body mass index
IQR, interquartile range
WHO, World Health Organisation

7.3 Measurements of Treatment Compliance

Not applicable.

7.4 Efficacy Results and Tabulations of Individual Patient Data

7.4.1 Analysis of efficacy

Primary efficacy endpoint, response, was defined as a proportion of patients who achieve platelet count ≥50x10^9/L in 2 measurements (taken at least 24 hours apart) during week 12 for patients in safety run-in and cohort 1, and week 16 for patients in cohort 2, without having received rescue therapy for the last 4 weeks, nor having had dose increment of TPO-RA or corticosteroids during the study period.

The primary endpoint was met in 10 patients (48%; 95% CI: 25.7-70.2), including 2/3 patients in the safety run-in, 4/9 patients (44%; 95% CI: 13.7-78.8) in cohort 1, and 4/9 patients (44%; 95% CI: 13.7-78.8) in cohort 2.One additional patient in Cohort 1 responded shortly after the primary endpoint evaluation, at week 14, with true overall response rate of 52%.

Secondary efficacy endpoints:

- Sustained response defined as defined as platelet count ≥ 50x10^9/L in 2 measurements (taken at least 24 hours apart) measured at study week 24 (+/-2 weeks) without having

received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids. A sustained response at week 24 was achieved in eight patients (38%, 95% CI: 18.1-61.6), one from the safety run-in, 4 (44%, 95% CI: 13.7-78.8) from Cohort 1, and three (33%, 95%: CI 7.4-70.0) from Cohort 2.

- Duration of response (DOR) was defined as duration of sustained platelet count $\geq 50x10^9/L$ without having received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids. Duration will not consider the 4 weeks following the last daratumumab injection in the study. Loss of response is defined as platelet count $< 50 \times 10^9/L$ after achieving response, in 2 consecutive blood samples taken at least 24 hours apart. Median DOR was 653 days (range, 35-1010) in the whole study population, 568 days (range, 96-798) in cohort 1, and 246 days (range, 35-351) in cohort 2.
- Time to treatment failure was defined as the time with platelet count$\geq 50x10^9/L$ from 4 weeks after the last daratumumab injection to the first platelet count $<30x10^9/L$ of two counts taken in two consecutive measurements at least 24 hours apart, or administration of any platelet elevating therapy after achieving response. Date of first platelet count measurement or administration of platelet elevation therapy will be used for the calculation of TTF. Median TTF was 680 days (range, 35-1010) in whole study population, 568 days (range, 365- 798) in cohort 1, and 246 days (range, 35-351) in cohort 2.
- Bleeding complications: Seven patients experienced bleeding episodes; all were WHO grade 2, and none were related to treatment. One patient experienced macroscopic hematuria and another experienced menorrhagia. Detailed overview is presented in Appendix 12.7.

Exploratory efficacy endpoints:

- Time to first platelet count $>50x10^9/L$ measured from the day of first administration of study medication. Eighteen (86%) patients achieved a platelet count of $\geq 50x10^9/L$ at least once between the date of the first study treatment and the primary endpoint evaluation with median time to first platelet count $\geq 50x10^9/L$ of 7 days (range, 6-10).
- Rates of complete response defined as a proportion of patients with platelet count $\geq 100x\ 10^9/L$ determined at week 12 for the safety run-in and cohort 1, week 16 for cohort 2, and at week 24 for all patients, without having received rescue therapy

after week 8 or having had dose increment of corticosteroids or TPO-RA during the study period. In total, at the point of the primary efficacy endpoint evaluation, 9 patients (43%, 95% CI 21.8-66.0) achieved complete response; 2 in safety run-in, 3 (33%, 95% CI 7.4-70.0) in cohort 1, and 4 (44%, 95% CI 13.7-78.8) in cohort 2. At week 24, 7/21 patients (33%, 95% CI 14.6-57.0) were in complete response; 1 in safety run-in, 3/9 (33%, 95% CI 7.4- 70.0) in both cohort 1 and cohort 2.

- Rates of partial response defined as a proportion of patients with platelet count >30 x 10^9/ but <50x 10^9/L (or at least doubling of the platelet count from baseline, determined at week 12 for the safety run-in and cohort 1, week 16 for cohort 2, and at week 24 for (requires two measurements taken at least 24 hours apart) without having received rescue therapy after week 8, or having had dose increment of corticosteroids or TPO-RA during the study period. In total, only 1 patient (5%, 95% CI 0.1-23.0) achieved partial response (cohort 2).

7.4.2 Statistical/ analytical issues

Detailed description of statistical analysis is given in statistical analysis plan (SAP v1.0), attachment 2.

7.4.2.1 Adjustments of covariates

No adjustments were done.

7.4.2.2 Handling of dropouts and missing data

No replacement of missing data was done except for the estimation of platelet level at a given visit; where the last evaluation before the visit (if none is available at the visit) will be used until study week 24.

The method of last observation carried forward (LOCF) was used for the analysis of the evolution of platelet count. However, a missing platelet count, after a patient has been definitely classified as R (response)=no, was be replaced and was kept as missing.

If patient was categorized as sR (sustained response) =yes at week 24, response evaluation at time of EOS was done by two independent members of steering committee if there is missing values on the platelet level at one or several points of evaluation defined by study protocol.

For all other presentations and analyses, LOCF was not used, and so subjects with missing values of a particular endpoint did not contribute to the analysis.

7.4.2.3 Interim analyses.
No interim analyses were performed.

7.4.2.4 Multicenter studies
Due to the low number of participants no separate data analysis sets presented for each center.

7.4.2.5 Multiple comparisons/multiplicity
Not applicable

7.4.2.6 Use of "Efficacy subset" of patients
Not applicable

7.4.2.7 Active-control studies intended to show equivalence
Not applicable

7.4.2.8 Examination of subgroups
Results of efficacy analyses for cohort 1 and 2 are presented in 7.4.1. No separate analyses were done in safety run-in due to a very low number of patients in this subgroup.

7.4.3 Tabulation of individual response data
Individual responses for primary and secondary efficacy endpoints presented in Appendix 12.8

7.4.4 Drug dose and relationships to response.
All patients received daratumumab 1800 mg as a single dose. Total dose of daratumumab given to each patient during the treatment period depended on treatment group. Three patients in safety run-in received total of 4 daratumumab injections, 1800 mg each; 9 patients in cohort 1 received total of 8 daratumumab injections, 1800 mg each, and 9 patients in cohort 2 received total of 10 daratumumab injections, 1800 mg each.
The number of patients in this study and in each treatment, group is too small to perform a reliable analyses of differences in efficacy depending on the total dose of daratumumab. In addition, in order to compare, the number of patients in safety run-in is considerably different from the number of patients in cohort 1 and cohort 2.
However, based on the results, there were no difference in response and relapse rates between the cohorts.

It is possible that the difference between the number of injections in cohort 1 and cohort 2 was also too small to affect response rates and the duration of responses.

7.4.5 Drug-drug and drug-disease interactions

In this study, glucocorticoids (methylprednisolone or equivalent) were used as premedication before each study drug treatment. The use of glucocorticoids have a potential to affect platelet responses, and may, at least partly, explain the initial increase in platelet counts to $\geq 50x10^9$/L in 86% of study participants during the first weeks after treatment initiation.
To minimaze a possible effect of corticosteroid premedication on platelet counts, the primary efficacy endpoint was evaluated at week 12 for the safety run-in and Cohort 1, week 16 for Cohort 2.

7.4.6 Efficacy conclusions

Daratumumab was effective in 52% of patients with sustained response of 38%. Responses appeared to diminish over time.
This results establish the efficacy of the CD38 antibody daratumumab in ITP patients who failed multiple lines of therapy. The 38% sustained response rate compares very favorably with any other novel treatments such as rilzabrutinib (23%), efgartigimod (22%), and fostamatinib (18%).

8. Safety Evaluation

8.1 Extent of exposure

Duration:

- Safety run-in: each of 3 patients received 1 dose (injection) of daratumumab once weekly, a total of 4 weeks per patient.
- Cohort 1: each of 9 patients received 1 dose (injection) of daratumumab once weekly, a total of 8 weeks per patient
- Cohort 2: each of 9 patients received 1 dose (injection) of daratumumab once weekly, for 8 weeks, and thereafter 1 dose (injection) of daratumumab every other week for 2 weeks; a total of 12 weeks treatment per patient.

Dose: each patient in each cohort received subcutaneous daratumumab 1800 mg/dose.

- Safety run-in: a total of 3 doses.
- Cohort 1: a total of 8 doses.
- Cohort 2: a total of 10 doses.

Cumulative subject exposure in the study presented in Appendix 12.9.

8.2 Adverse events

8.2.1 Brief summary of adverse events and display of adverse events

Daratumumab was generally well tolerated, with a safety profile consistent with previous studies in patients with plasma cell disease. No unexpected side effects were observed in patients with primary ITP, and no cases of worsening thrombocytopenia were reported after treatment initiation.

Treatment-Emergent Adverse Events (TEAEs)

An overview of TEAEs is provided in Table 2.

The majority were grade 1–2. Three grade 3 TEAEs occurred in two patients: one infusion-related reaction (considered a treatment-related adverse event by the investigator) and one case of SARS-CoV-2 infection complicated by acute renal failure (deemed unrelated to the study treatment, as such infections were common during the COVID-19 pandemic).

Table 2. Summary of Treatment-Emergent Adverse Events.

Treatment-emergent adverse events (due to any case) *Number of patients (percent)*				
	Any grade	**Grade 1**	**Grade 2**	**Grade 3**
Any TEAE	20 (95)	16 (76.2)	15 (71.4)	2 (9.5)
Blood and lymphatic system				
Anemia	1 (4.7)	1 (4.7)	0	0
Bone marrow reticulin fibrosis	1 (4.7)	0	1 (4.7)	0
Eye disorders				
Blurred vision	1 (4.7)	1 (4.7)	0	0
Gastrointestinal disorders				
Vomiting	4 (19.0)	3 (14.3)	1 (4.7)	0
Diarrhea	3 (14.2)	1 (4.7)	2 (9.5)	0
Abdominal pain	2 (9.5)	1 (4.7)	1 (4.7)	0
Dyspepsia	2 (9.5)	2 (9.5)	0	0
Abdominal hernia	1(4.7)	1 (4.7)	0	0
Nausea	1 (4.7)	0	1 (4.7)	0
General disorders and administration site conditions				
Fever	5 (23.8)	3 (14.3)	2 (9.5)	0
Influenza-like symptoms	3 (14.2)	3 (14.2)	0	0
Edema of lower extremity	1 (4.7)	0	1(4.7)	0
Fatigue	1 (4.7)	0	1(4.7)	0
Injection site discoloration	1(4.7)	1(4.7)	0	0

Hepatobiliary disorders				
Increase in alkaline phosphatase	1(4.7)	1(4.7)	0	0
Infections and infestations				
Coronavirus infection	3 (14.3)	2 (9.5)	2 (9.5)	1 (4.7)
Nasopharyngitis	3 (14.3)	2 (9.5)	1 (4.7)	0
Upper respiratory tract infection	4 (19.0)	2 (9.5)	2 (9.5)	0
Sinusitis	2 (9.5)	1(4.7)	1 (4.7)	0
Otitis media	1 (4.7)	-	1 (4.7)	0
RS virus infection	1(4.7)	1(4.7)	0	0
Urinary tract infection	1 (4.7)	0	1 (4.7)	0
Inguinal abscess	1 (4.7)	1 (4.7)	0	0
Injury, poisoning and procedural complications				
Infusion related reaction	1(4.7)	0	0	1(4.7)
Procedural bleeding	1 (4.7)	0	1(4.7)	0
Contusion	1 (4.7)	0	1(4.7)	0
Lower limb fracture	1 (4.7)	0	1 (4.7)	0
Joint injury	1 (4.7)	0	1 (4.7)	0
Metabolism and nutritional disorders				
Weight gain	1 (4.7)	1 (4.7)	0	0
Musculoskeletal and connective tissue disorders				
Arthralgia	2 (9.5)	1 (4.7)	1 (4.7)	0
Neck pain	1 (4.7)	1 (4.7)	0	0
Muscle spasms	1 (4.7)	1 (4.7)	0	0
Nervous system disorders				
Headache	3 (14.2)	1 (4.7)	2 (9.5)	0
Head discomfort	1 (4.7)	1 (4.7)	0	0
Dizziness	1 (4.7)	1(4.7)	0	0
Paresthesias	1(4.7)	1 (4.7)	0	0
Psychiatric disorders				
Insomnia	2 (9.5)	1 (4.7)	1(4.7)	0
Renal and urinary disorders				
Acute kidney failure	1 (4.7)	0	0	1 (4.7)
Hematuria	1 (4.7)	1 (4.7)	0	0
Reproductive system and breast disorders				
Semen discoloration	1 (4.7)	1 (4.7)	0	0
Uterine prolapse	1 (4.7)	0	1 (4.7)	0
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	2(9.5)	1 (4.7)	1 (4.7)	0
Nasal congestion	1 (4.7)	1 (4.7)	0	0
Skin and subcutaneous tissue disorders				
Pruritus	3 (14.2)	3 (14.2)	0	0
Erythematous rush	2 (9.5)	2 (9.5)	0	0
Urticaria	1 (4.7)	0	1 (4.7)	0
Rush maculo-papular	1 (4.7)	1 (4.7)	0	0
Acne	1 (4.7)	1 (4.7)	0	0
Erythema face	1 (4.7)	1 (4.7)	0	0
Fungal infection, foot	2 (9.5)	2(9.5)	0	0
Fungal infection, nail	1 (4.7)	1 (4.7)	0	0
Fungal infection, skin	1 (4.7)	1 (4.7)	0	0
Ecchymoses	1 (4.7)	0	1 (4.7)	0
Vascular disorders				
Hypertension	1 (4.7)	0	1 (4.7)	0
Thrombophlebitis	1 (4.7)	0	1 (4.7)	0
Bleeding	1 (4.7)	0	1 (4.7)	0

Treatment- related adverse events(TRAE)

Relatedness to treatment in our study was determined by the study investigators. Most common TRAE`s were IRR (14.3%), injection site reactions (9.5%), infections (9.5%) and diarrhea (9.5%). Four patients had >1 TRAE.

Most TRAE were of grade 1-2 with only 1 TRAE (IRR) being of grade 3. All TRAE`s resolved.

Overview over TRAE is presented in Table 3

Table 3. Summary of treatment related adverse events

Treatment-related adverse events *Number of patients (percent)*				
	Any grade	**Grade 1**	**Grade 2**	**Grade 3**
Any adverse event	9 (42.9)	4 (19.0)	5 (23.8)	1 (4.7)
Infusion-related reactions	3 (14.3)	0	2 (9.5)	1 (4.7)
Injection site reaction	2 (9.5)	2 (9.5)	0	0
Infections	2 (9.5)	1 (4.7)	1 (4·7)	0
Diarrhea	2 (9·5)	0	2 (9·5)	0
Headache	1 (4·7)	1 (4·7)	0	0
Nausea	1 (4·7)	0	1 (4·7)	0
Vomiting	1 (4·7)	0	1 (4·7)	0
Weight gain	1 (4·7)	1 (4·7)	0	0

Serious adverse events

In total, six patients experienced seven SAE. Two patients experienced three grade 3 SAE (described under "TEAE").

All other SAE were of grade 2 (one patient with bleeding, one- procedural bleeding, one- headache and one had fever after the first daratumumab injection) but required hospital admission for observation and/or.

There were no SUSAR during the study.

Adverse events of special interest(AESI)

AESI are events that the company (Janssen) actively monitors as a result of a previously identified signal (even if non-serious).

Those were:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4 (except thrombocytopenia)
- HBV Reactivation
- Any malignancy

There were only 1 AESI during the study period (IRR grade 3).

8.2.2 Analysis of adverse events

In general, AE`s in the study were of minor severity, manageable and transient. There were no unexpected adverse events.

No subgroup analyses of adverse events for the 3 treatments groups (safety run-in, cohort 1 and cohort 2) were performed for this study.

8.2.3 Listing of adverse events by patient

Listing of adverse events by patient (by cohort) is presented in 10.1 and 10.2.

8.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred during the study period.

There were no other serious adverse events, or other significant adverse events that what have already been described.

8.4 Safety conclusions

Daratumumab demonstrated an acceptable safety profile in the ITP patient population, with no unexpected adverse events related to the study drug. The majority of adverse events were grade 1–2, with only three cases of grade 3.

Our findings align with previous studies on daratumumab, confirming its safety also in the ITP population.

9. Discussion and overall conclusions

The study demonstrated that daratumumab is both safe and effective in a heavily pre-treated ITP population. Overall, the treatment was well tolerated:

Safety:

- All 21 enrolled patients completed the study, with no treatment discontinuations due to adverse events.
- Treatment-emergent adverse events were predominantly mild to moderate (grade 1–2), with only two patients experiencing grade 3 events. One event was an infusion-related reaction, and the other, a SARS-CoV-2 infection complicated by acute renal failure, was deemed unrelated to the study treatment.
- There were no grade 4 events, thrombotic events, or deaths, and no unexpected side effects were observed.
- The overall safety profile was consistent with previous studies in patients with plasma cell disease.

Efficacy:

- The primary endpoint of response was met by approximately 48% of patients, with an overall response rate potentially reaching 52% when including a late responder.
- A sustained response at week 24 was observed in 38% of patients, with a median duration of response of 653 days and a median time to treatment failure of 680 days.
- Importantly, all responding patients were able to discontinue concomitant ITP-directed medications, with a median discontinuation time of six weeks.

Overall, the findings support the use of daratumumab as a promising therapeutic option for patients with primary ITP, particularly for those who are non-splenectomized and have undergone multiple previous ITP-directed therapies.

10. Tables not included in the text

10.1 Overview over patients characteristics

Cohort	Subject ID	Sex	Age (years)	Weight (kg)
Safety run-in	NO-01-01	M	75	96
	NO-01-02	F	33	93
	NO-04-01	M	55	146
Cohort 1	NO-01-03	M	67	84
	NO-01-04	M	75	103
	NO-02-01	F	51	77.8
	NO-02-02	F	41	98
	NO-02-03	M	25	86
	NO-03-01	F	34	81.5
	NO-03-02	M	36	112
	NO-03-03	M	65	90.5
	NO-04-02	F	77	57
Cohort 2	NO-01-05	F	49	95.3
	NO-02-04	M	59	90
	NO-03-04	M	73	92.2
	NO-04-03	M	57	80.1
	DK-01-01	M	33	138
	DK-01-02	M	62	110
	DK-01-03	M	40	61
	DK-01-04	F	19	64
	FR-01-01	M	30	78

M, male; F, female

10.2 Listing of adverse events by patient (by cohort)

A. Safety run-in- patients in this group received 4 weekly daratumumab injections à 1800 mg each (W1-W4)

Site	Subject Id	Event date	AE term	Start date	AE End Date	AE CTCAE grade	SAE	Start during IMP administration?	Related to study treatment?	Adjunct Therapy	Concomitant Therapy	Whas action taken with study treatment?	Concomitant or additional treatment due to AE?	What was the outcome of this AE?
Haukeland University Hospital	NO-04-01	2021-04-19	urticaria	2021-04-09	2021-04-10	Moderate	No	No	R	No	No	No		Resolved
		2021-11-02	nasal congestion	2021-06-NK	2023-04-13	Mild	No	No	NR	No	No	No	No	Resolved
		2021-11-02	Hypertension	2021-09-NK		Moderate	No	No	NR	No	No	No		Resolving
		2021-11-02	paresthesias	2021-06-NK	2023-04-13	Mild	No	No	NR	No	No	No	No	Resolved
Østfold Hospital	NO-01-01	2021-04-18	Dizziness	2021-01-27	2021-02-04	Mild	No	No	NR	No	Yes	No	No	Resolved
		2021-08-24	Fever	2021-03-05	2021-03-05	Mild	No	NA	NR	No	No	NA	No	Resolved
Østfold Hospital	NO-01-02	2021-06-22	Red rash	2021-06-10	2021-06-15	Mild	No	Yes	R	No	No	No	No	Resolved
		2021-06-24	Red rash	2021-06-17	2021-06-19	Mild	No	No	R	No	No	No	No	Resolved
		2021-10-26	Pruritus	2021-09-30		Mild	No	No	NR	No	No	NA	No	Not resolved

AE, adverse event; SAE, serious adverse events; CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product;
R, related; NR, non-related; NA, not applicable

B. Cohort 1: patients received 8 weekly subcutaneous daratumumab injections à 1800 mg each (W1-W8)

Site	Subject Id	Event date	AE term	Start date	AE End Date	AE CTCAE grade	SAE	Start during IMP administration?	Related to study treatment?	Adjunct Therapy	Concomitant Therapy	Whas action taken with study treatment?	Concomitant or additional treatment due to AE?	What was the outcome of this AE?
Akershus University Hospital	NO-03-01	2021-10-07	Blurred vision	2021-09-30	2021-09-30	Mild	No	No	NR	No	No	No	No	Resolved
		2021-10-07	Body itch	2021-09-24	2021-12-16	Mild	No	No	NR	No	No	No	No	Resolved
		2021-10-14	Flulike symptoms	2021-10-12	2021-10-16	Mild	No	No	NR	No	No	NA	No	Resolved
		2021-10-27	Abdominal pain	2021-10-17	2021-10-18	Mild	No	No	NR	No	No	No	No	Resolved
		2021-10-27	Fever	2021-10-18	2021-10-19	Mild	No	No	NR	No	No	No	No	Resolved
		2021-10-28	Flu like symptoms	2021-09-26	2021-09-30	Mild	No	No	NR	No	No	No	No	Resolved
		2021-11-04	Vomiting	2021-11-01	2021-11-01	Mild	No	No	NR	No	No	No	No	Resolved
		2021-11-11	Flu like symptoms	2021-11-08	2021-12-08	Mild	No	No	NR	No	No	NA	No	Resolved
Oslo University Hospital	NO-02-01	2021-10-20	Infusion related reaction	2021-10-19	2021-10-19	Severe	Yes	No	R	No	No	No		Resolved
		2021-10-26	Headache	2021-10-21	2021-10-21	Moderate	No	No	NR	No	No	No		Resolved
		2021-10-26	Headache	2021-10-23	2021-10-23	Moderate	No	No	NR	No	No	No		Resolved
		2021-10-26	Pain in neck	2021-10-26	2021-NK-NK	Mild	No	No	NR	No	No	No	No	Resolved

		2021-11-23	common cold	2021-11-17	2021-11-NK	Mild	No	No	NR	No	No	No		Resolved
		2022-01-18	Common cold	2022-01-18	2022-01-NK	Mild	No	NA	NR	No	No	NA	No	Resolved
		2022-02-15	Covid infection	2022-02-10	2022-04-NK	Moderate	No	NA	NR	No	No	NA		Resolved
		2022-06-16	Common cold	2022-06-10	2022-06-19	Mild	No	No	NR	No	No	NA	No	Resolved
		2023-03-01	Covid 19 infection	2022-10-NK	2022-10-NK	Mild	No	No	NR	No	No	NA	No	Resolved
		2023-09-19	Common cold	2023-01-NK	2023-01-NK	Mild	No	No	NR	No	No	NA	No	Resolved
		2023-12-13	Common cold	2023-11-07	2023-11-14	Mild	No	No	NR	No	No	No	No	Resolved
		2024-03-22	RS virus	2024-03-04	2024-03-10	Mild	No	No	NR	No	No	No	No	Resolved
	NO-02-02	2021-10-26	Nausea	2021-10-19	2021-10-20	Moderate	No	No	R	No	No	No	No	Resolved
		2021-10-26	vomiting	2021-10-19	2021-10-20	Moderate	No	No	R	No	No	No	No	Resolved
		2021-10-26	Diarrhea	2021-10-19	2021-10-20	Moderate	No	No	R	No	No	No	No	Resolved
		2021-11-09	Dyspepsia	2021-11-09	2021-12-NK	Mild	No	No	NR	No	No	NA		Resolved
		2022-06-21	soft tissue damage in left knee	2022-06-03	2022-06-13	Moderate	No	No	NR	No	No	NA	No	Resolved

Østfold Hospital	NO-01-03	2023-03-24	Fever	2022-12-22	2022-12-30	Moderate	No	No	NR	No	No	NA		Resolved
Østfold Hospital	NO-01-04	2022-01-06	Bleeding	2021-12-21	2021-12-24	Moderate	Yes	No	NR	No	No	NA		Resolved
Akershus University Hospital	NO-03-02	2022-03-24	Flu like symptoms	2022-03-22	2022-04-17	Mild	No	NA	NR	No	No	NA	No	Resolved
		2022-07-04	Flu like symptoms	2022-06-22	2022-07-01	Mild	No	NA	NR	No	No	NA	No	Resolved
		2023-10-24	Flu like symptoms	2023-10-16	2023-11-20	Mild	No	No	NR	No	No	NA	No	Resolved
Akershus University Hospital	NO-03-03	2022-03-14	SARS-CoV-2 infection	2022-03-11	2022-05-25	Moderate	Yes	No	NR	No	No	NA		Resolved
		2022-04-22	Acute kidney failure	2022-03-21	2022-04-05	Severe	Yes	No	NR	No	No	NA	No	Resolved
		2022-04-27	Diarrhea	2022-04-23	2022-04-28	Mild	No	No	NR	No	No	No	No	Resolved
		2022-04-27	Vomit	2022-04-23	2022-04-25	Mild	No	No	NR	No	No	No	No	Resolved
Haukeland University Hospital	NO-04-02	2022-05-31	uterine prolapse	2022-05-NK		Moderate	No	No	NR	No	No	No	No	Not resolved
		2022-05-31	lump in the epigastrium	2022-05-NK	2022-07-21	Mild	No	No	NR	No	No	No		Resolved
		2022-07-22	Bleeding from basal cell carcinoma upper left arm after treatment of the wound	2022-07-18	2022-07-19	Moderate	Yes	No	NR	No	No	NA		Resolved
		2022-07-22	Abdominal pain, worsening	2022-07-NK	2022-08-05	Moderate	No	No	NR	No	No	NA	No	Resolved

		2022-08-17	Bleeding from basal cell carcinoma upper left arm after treatment of the wound	2022-06-NK		Moderate	No	No	NR	No	No	No	No	Not resolved
		2022-08-17	cramp in the hands	2022-06-NK		Mild	No	No	NR	No	No	No	No	Not resolved
		2022-10-10	ecchymoses	2022-10-03		Moderate	No	No	NR	No	No	NA	No	Not resolved

AE, adverse event; SAE, serious adverse events; CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product.
R, related; NR, non-related; NA, not applicable

C. Cohort 2 patients received 8 weekly subcutaneous daratumumab injections followed by to bi-weekly injections à 1800 mg each (W1-W12)

Site number	Subject Id	Event date	AE term	Start date	AE End Date	AE CTCAE grade	SAE	Start during IMP administration?	Related to study treatment?	Adjunct Therapy	Concomitant Therapy	Whas action taken with study treatment?	Concomitant or additional treatment due to AE?	What was the outcome of this AE?
Oslo University Hospital	NO-02-04	2022-11-14	diarrhea	2022-11-05	2022-11-06	Moderate	No	No	R	Yes	No	No	No	Resolved
		2022-11-21	Covid 19 infection	2022-11-20	2022-11-NK	Mild	No	No	NR	No	No	NA	No	Resolved
		2023-03-03	Flu	2023-02-24	2023-02-26	Mild	No	No	NR	No	No	NA	No	Resolved
		2023-04-17	mucosal bleeding	2023-04-08	2023-04-09	Moderate	No	No	NR	No	No	NA		Resolved
		2023-05-04	common cold	2023-03-NK	2023-03-NK	Moderate	No	No	NR	No	No	NA	No	Resolved
		2023-12-13	Fever	2022-12-01	2022-12-NK	Mild	No	No	NR	No	No	No	No	Resolved
Haukeland University Hospital	NO-04-03	2022-12-04	pressure in the head/above the maxillary sinus	2022-11-05	2022-11-16	Mild	No	No	NR	No	No	No	No	Resolved
		2022-12-04	viral cold	2022-11-16	2022-11-23	Mild	No	No	NR	No	No	No	No	Resolved
		2022-12-04	Epistaxis	2022-11-22	2022-11-22	Mild	No	No	NR	No	No	No	No	Resolved
		2022-12-21	Insomnia	2022-12-15	2022-12-16	Mild	No	No	NR	No	Yes	No	No	Resolved

		2022-12-21	Epistaxis	2022-12-21	2022-12-21	Mild	No	No	NR	No	No	No	No	Resolved
		2023-01-04	Epistaxis	2022-12-27	2022-12-27	Mild	No	No	NR	No	No	No	No	Resolved
		2023-01-04	pain in joints	2022-12-29		Mild	No	No	NR	No	No	No	No	Not resolved
		2023-01-18	Epistaxis	2023-01-17	2023-01-17	Mild	No	No	NR	No	No	No		Resolved
		2023-03-21	hematuria	2023-03-NK	2023-03-NK	Mild	No	No	NR	No	No	No	No	Resolved
		2023-03-21	Fatigue	2023-03-NK		Moderate	No	No	NR	No	No	No	No	Not resolved
		2023-04-13	Fracture in right leg	2023-02-09	2023-04-13	Moderate	No	No	NR	No	No	No		Resolved
		2023-06-27	Headache	2023-06-09	2023-06-13	Moderate	Yes	No	NR	No	No	No		Resolved
Odense University Hospital	DK-01-01	2023-01-30	Fungus in hands	2023-01-30	2023-02-06	Mild	No	No	NR	No	No	No		Resolved
		2023-04-25	Otitis media	2023-04-21	2023-05-08	Moderate	No	No	NR	No	No	No		Resolved
		2023-06-19	edema of lower right extremity	2023-05-29	2023-06-12	Moderate	No	No	NR	No	No	No	No	Resolved
		2023-08-08	abscess in right inguen	2022-12-22	2022-12-29	Mild	No	No	NR	No	No	No	No	Resolved
		2023-12-19	weight gain	2023-02-13	2023-06-NK	Mild	No	No	R	No	No	No	No	Resolved
		2024-01-08	Sinusitits	2024-01-08	2024-01-13	Moderate	No	NA	NR	No	No	NA		Resolved

		2024-04-09	foot fungus	2023-01-30	2023-02-06	Mild	No	NA	NR	No	No	No		Resolved
Odense University Hospital	DK-01-02	2023-03-24	Insomnia	2023-03-20	2023-05-15	Moderate	No	No	NR	No	Yes	No	No	Resolved
Odense University Hospital	DK-01-03	2023-11-14	Nail fungus	2023-08-31		Mild	No	NA	NR	No	No	NA		Not resolved
		2023-11-14	foot fungus	2023-08-31		Mild	No	NA	NR	No	No	NA		Not resolved
Akershus University Hospital	NO-03-04	2023-03-29	Fever	2023-03-28	2023-03-29	Moderate	Yes	Yes	R	No	No	No		Resolved
	NO-03-04	2023-04-12	Thrombophlebitis	2023-04-12	2023-06-12	Moderate	No	No	NR	No	No	No		Resolved
Østfold Hospital	NO-01-05	2023-04-11	Headache	2023-04-04	2023-04-04	Mild	No	Yes	NR	No	No	No	No	Resolved
		2023-04-11	Red rash	2023-04-04	2023-04-06	Mild	No	No	R	No	No	No	No	Resolved
		2023-04-11	headache	2023-04-11	2023-04-11	Mild	No	Yes	NR	No	No	No	No	Resolved
		2023-04-19	Heartburn	2023-04-11	2023-04-30	Mild	No	No	NR	No	Yes	No		Resolved
		2023-04-26	Headache	2023-04-19	2023-04-19	Mild	No	No	R	No	No	No	No	Resolved
		2023-04-26	Pain in the buttock	2023-04-22	2023-05-11	Moderate	No	NA	NR	No	No	No		Resolved
		2023-04-26	Pimples	2023-04-23	2023-05-24	Mild	No	NA	NR	No	No	No	No	Resolved
		2023-05-03	Headache	2023-04-26	2023-04-26	Mild	No	No	NR	No	No	No	No	Resolved
		2023-05-10	White area on abdomen after injection	2023-05-04	2023-05-05	Mild	No	No	R	No	No	No	No	Resolved

		2023-05-22	Flaming red in the face	2023-04-05	2023-06-23	Mild	No	No	NR	No	No	No	No	Resolved
		2023-05-24	Headache	2023-05-22	2023-05-22	Mild	No	No	NR	No	No	No		Resolved
		2023-06-08	Upper respiratory tract infection	2023-05-29	2023-05-30	Mild	No	No	NR	No	No	No	No	Resolved
		2023-06-08	Headache	2023-06-05	2023-06-05	Mild	No	No	NR	No	No	No		Resolved
		2023-07-05	cold	2023-07-02	2023-07-15	Mild	No	No	NR	No	No	NA	No	Resolved
		2023-09-05	Pain in large joints	2023-08-29		Moderate	No	No	NR	No	No	NA		Not resolved
Odense University Hospital	DK-01-04	2023-03-31	sinusitis	2023-03-31	2023-04-11	Mild	No	No	R	No	No	NA		Resolved
		2023-04-25	maculopapular rash cheeks	2023-04-20	2023-05-02	Mild	No	No	NR	No	No	No	No	Resolved
		2023-05-03	Sinusitis	2023-04-30	2023-05-15	Mild	No	No	R	No	No	No		Resolved
		2023-08-09	upper respiratory tract infection	2023-07-13	2023-07-14	Moderate	No	No	R	No	No	NA		Resolved
		2023-09-11	Urinary tract infection	2023-08-29	2023-09-04	Moderate	No	No	NR	No	No	NA		Resolved
Henry Mondor University Hospital	FR-01-01	2023-10-12	Pruritus	2023-10-05	2023-10-06	Mild	No	No	NR	No	No	No	No	Resolved
		2023-11-09	Vomiting	2023-10-27	2023-10-27	Mild	No	No	NR	No	No	No	No	Resolved
		2023-11-09	Dysphagiant angina	2023-10-26	2023-10-30	Moderate	No	No	NR	No	No	No		Resolved
		2023-11-24	Sperm color change	2023-11-NK	2024-01-04	Mild	No	No	NR	No	No	No	No	Resolved

		2024-01-05	Anemia	2023-12-21	2024-03-29	Mild	No	NA	NR	No	No	No	No	Resolved
		2024-02-15	Myelofibrosis	2024-01-26		Moderate	No	No	NR	No	Yes	NA	No	Not resolved
		2024-03-18	Increase of alcaline phosphatase	2023-11-16	2024-02-01	Mild	No	No	NR	No	No	No	No	Resolved

AE, adverse event; SAE, serious adverse events; CTCAE, Common Terminology Criteria for Adverse Events; IMP, investigational medicinal product.
R, related; NR, non-related; NA, not applicable

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12. Appendix

12.1 Independent Ethics Committee (IEC)

- Norway: Regionale Komiteer for Medisinsk Og Helsefaglig Forskningetikk
  Record number REK Sør-Øst 7193
  Committee Chair: Erik Fosse
- Denmark: De Videnskapsetiske Medisinske Komiteer
  Record number 2207507
  Committee Chair: Tarec Christoffer EL- Galaly
- France: Comite De Protection Des Personnes Sud Mediterranee III
  Record number 2022.03.08 bis_22.00301.000070
  Committee Chair: J-Y. Lefrant

12.2 Investigators and administrative study structure

Coordinating investigator:

Waleed Ghanima Prof.,MD, PhD

Department of Hematology-Oncology, Østfold Hospital Trust, Kalnes, Norway

List of Investigators by Country

Country	Institution	Role in study	Name,
Norway	Østfold Hospital Trust, Kalnes	Principal Investigator Study Nurse	Waleed Ghanima Heidi Hassel Pettersen
	Oslo University Hospital , Oslo	Principal Investigator Study Nurse	Pål Andre Holme Vilma Naujokaite
	Akershus University Hospital, Oslo	Principal Investigator Study nurse	Hoa Tran Øyvind Øverli
	Haukeland University Hospital	Principal Investigator Study nurse	Galina Tsykunova Kristin Eikevåg
Denmark	Odense University Hospital	Principal Investigator Study nurse	Henrik Frederiksen Pernille Sonnenborg Pedersen
France	Henry Mondor University Hospital	Principal Investigator Study nurse	Marc Michel Laetitia Languille

Steering Committee:

Member	Affiliation
Waleed Ghanima Prof., MD, PhD	Department of Hematology-Oncology, Østfold Hospital Trust, Kalnes, Norway
Pål Andre Holme Prof., MD, PhD	Department of Hematology, Oslo University Hospital, Oslo, Norway
Tor Henrik Anderson Tvedt MD, PhD	Department of Hematology, Oslo University Hospital, Oslo, Norway
Hoa Tran MD	Department of Hematology, Akershus University Hospital, Oslo, Norway
Galina Tsykunova MD	Department of Medicine, Division of Hematology, Haukeland University Hospital, Bergen, Norway
Marc Michel Prof., MD, PhD	Service de Médecine Interne 1, Centre de Référence des Cytopénies Auto-Immunes de l'Adulte, Centre Hospitalo-Universitaire Henri Mondor, Créteil, France
Henrik Frederiksen Prof., MD, PhD	Department of Hematology, Odense University Hospital, Odense, Denmark
James Bussel Prof.,MD, PhD	Department of Pediatrics, Weill Cornell Medicine, New York, USA
David J Kuter Prof., MD, PhD	Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, USA

Data safety and Monitoring Board (DSMB)

Member	Affiliation
Anders Waage Professor Emeritus, MD, PhD	Institute of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway.
Sigbjørn Berentsen MD, PhD	Department of Research and Innovation, Haugesund Hospital, Helse Fonna Hospital Trust, Haugesund, Norway

Medical Monitor:

Hilde Skuterud Wik MD, PhD; Department of Hematology, Oslo University Hospital, Oslo, Norway.

Central Laboratory Facilities:

Ludvig Andre Munthe Prof., MD, PhD; KG Jebsen Centre for B cell Malignancies and Precision Immunotherapy Alliance (PRIMA), Department of Immunology, Institute of Clinical Medicine, University of Oslo and Oslo University Hospital

Thrombocyte antibodies analysis:

Ingvild Hausberg Sørvoll MD**;** Norwegian National Unit for Platelet Immunology, Department of Laboratory Medicine, University Hospital of North Norway, Tromsø, Norway

Maria Therese Ahlen PhD; Norwegian National Unit for Platelet Immunology, Department of Laboratory Medicine, University Hospital of North Norway, and Institute of Medical Biology, UiT the Arctic University of Norway; Tromsø, Norway

The author of the report:

Galina Tsykunova MD, Department of Medicine, Division of Hematology, Haukeland University Hospital, Bergen, Norway

12.3 Listing of investigational product (batches)

CEMS Item Code	Item Name	Entry number	LOT	Expiration date	CEMS Project ID
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2020120315043815	BE20800378	02-Dec-2021	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2021071212333760	BE21800362	02-Jul-2022	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2021080309270616	BE21800419	02-Jul-2022	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2021100711110782	BE21800518	02-Jul-2022	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2022032909033541	BE22800130	01-Mar-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2022090614163962	BE22800468	01-Mar-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2022101709002188	BE22800468	01-Mar-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2023021615552859	BE23800016	07-Jul-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2023031714481267	BE23800163	02-Dec-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2023041716442236	BE23800163	02-Dec-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2023041815241014	BE23800205	02-Dec-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2023052512265536	BE23800205	02-Dec-2023	144-20-039
0022495	Daratumumab 1800 mg (120 mg/ml) SC, box containing 1 vial labelled for protocol RGCH005	SSU2023092608471338	BE23800466	05-Apr-2024	144-20-039

12.4 Randomization scheme and codes (patient identification and treatment assigned)

Study phase	Treatment	Patient codes
Safety run-in	Daratumumab injection (1800 mg), 4 weekly doses	NO-01-01; NO-01-02; NO-04-02
Cohort 1	Daratumumab injection (1800 mg) 8 weekly doses	NO-01-03; NO-01-04; NO-02-01; NO-02-02; NO-02-03; NO-03-01; NO-03-02; NO-03-03; NO-04-02
Cohort 2	Daratumumab injection (1800 mg), 8 weekly injection + 2 biweekly injections (total of 10 injections)	NO-01-04; NO-02-04; NO-03-04; NO-04-03; DK-01-01; DK-01-02; DK-01-03; DK-01-04; FR-01-01

12.5 Schedule of activities

	Safety run-in					
	Treatment			**Follow-up +/-1 week**		**Follow-up +/-2 weeks**
	Screening	**Baseline**	**Treatment weeks 1-4**	**Follow up weeks 5-22**	**Follow up week 24**	**Follow up / End of study***
Study timeline (weeks)	< 0	0	1,2,3,4	6,8,10,12,14,16,18,20,22	24	Every 4 weeks
Inclusion/exclusion criteria	x	x				
Informed consent	x					
Demographic data	x					
History of ITP		x				
Other medical history		x				
Physical examination		x			x	
Bleeding score[1]		X	x	x	x	x
Haematology[2] (local lab)	X and Haptoglobin, DAT		x	x	x	x
Blood sampling/biobank		week 0,4 and 12			x	
Platelet bound antibodies[9]		week 0 and 8			x	
Stool sampling		x				
Biochemistry[3] (local lab)		week 0 and 12			x	
Ig quantification[4] (local lab)		week 0 and 12			x	
Pregnancy test (if relevant[5]		x	x	x	x	x
Bone marrow sampling[6]		week 0 and 12				
HiV/ hepatitis tests	x					
Red cells antibody screening (local lab)		x				
Quality of life and fatigue[7]		x		x	x	
Concomitant therapies	x		x	x	x	x
Other treatment of ITP	x	x	x	x	x	x
Daratumumab injection			x			
AE/SAE			x	x	x	x

Immunogenicity (ADA)[8]		Blood samples for ADA measurement will be taken at weeks 1,4,8,12, 24

[1] World Health Organization Bleeding Assessment scale ± Khellaf bleeding score, [2] Haematology analyses: platelets, hemoglobin, White Blood Count with differential analysis. Two separate platelet counts measurements required at week 12 and 24(taken at least 24 hours but not longer than 7 days apart), [3] Blood analyses: LDH, ASAT, ALAT, bilirubin, creatinine, CRP, [4]IgG quantification must be taken at baseline, week 12, 24, [5] Pregnancy tests must be taken at baseline and then every 4 weeks and until three months after the last daratumumab injection and at the end of study visit, [6]Study samples at Oslo University hospital OUS (week 0,4,12,24, only Norwegian and French study centers) and biobanking (only Norwegian centers) in Ostfold Hospital Trust (week 0 and 24), [7] HRQoL, and fatigue will be recorded at baseline, at week 8 and 24 of follow up, [8]Blood sampling during treatment weeks should be taken before drug administration(only Norwegian centers), [9]only Norwegian centers, *last visit (atweek 24) for the last patient.

[**]Patients with no response will be followed only until study week 24. Participants with loss of response who require continued use of other ITP- directed therapies with be taken out of the study after week 24.

	Cohort 1					
	Treatment			**Follow-up +/-1 week**		**Follow-up +/-2 weeks**
	Screening	**Baseline**	**Treatment weeks 1-8**	**Follow up weeks 9-20**	**Follow up week 24**	**Follow up / End of study***
Study timeline (weeks)	< 0	0	1,2,3,4,5,6,7, 8	10,12,14,16,18,20, 22	24	Every 4 weeks
Inclusion/exclusion criteria	x	x				
Informed consent	x					
Demographic data		x				
History of ITP		x				
Other medical history		x				
Physical examination		x			x	
Bleeding score[1]		x	x	x	x	x
Haematology[2] (local lab)	x and Haptoglobin, DAT		x	x	x	x
Blood sampling/biobank		week 0,4 and 12			x	
Platelet bound antibodies[9]		week 0 and 12			x	
Stool sampling		x				
Biochemistry[3] (local lab)		week 0 and 12			x	
Ig quantification[4] (local lab)		Week 0 and 12			x	
Pregnancy test (relevant[5]		x	x	x	x	
bone marrow sampling[6]		week 0 and 12				
HiV/ hepatitis tests	x					
Red cells antibody screening (local lab)		x				
Quality of life and fatigue[7]		x		x	x	
Concomitant therapies	x	x	x	x	x	x
Other treatment of ITP	x	x	x	x	x	x
Daratumumab injection			x			
AE/SAE			x	x	x	x

Immunogenicity (ADA)[8]		Blood samples for ADA measurement will be taken at weeks 1,4,8,12, 24

[1] World Health Organization Bleeding Assessment scale ± Khellaf bleeding score, [2] Hematology analyses: platelets, hemoglobin, Complete Blood Count with differential analysis. Two separate platelet counts measurements required at week 12 and 24(taken at least 24 hours but not longer than 7 days apar[3] Blood analyses: LDH, ASAT, ALAT, bilirubin, creatinine, CRP, [4]IgG quantification must be taken at baseline, week 12, 24 [5] Pregnancy tests must be taken at baseline and then every 4 weeks and until three months after the last daratumumab injection and at the end of study visit, [6] Study samples at Oslo University hospital OUS (week 0,4,12,24, only Norwegian and French centers) and biobanking (only Norwegian centers) at Ostfold Hospital Trust (week 0 and 24),[7] HRQoL and fatigue will be recorded at baseline, week 12 and 24 of follow up, [8]Blood sampling during treatment weeks should be taken before drug administration(only Norwegian centers),[9]only Norwegian centers, *last visit (atweek 24) for the last patient.

[**]Patients with no response will be followed only until study week 24. Participants with loss of response who require continued use of other ITP- directed therapies with be taken out of the study after week 24.

	Cohort 2						
	Treatment				**Follow-up +/-1 week**		**Follow-up+/2 weeks**
	Screening	**Baseline**	**Treatment weeks 1-8**	**Treatment weeks 9-12**	**Follow up weeks 13-20**	**Follow up week 24**	**Follow up / End of study***
Study timeline (weeks)	< 0	0	1,2,3,4,5,6,7, 8	10,12	14, 16,18,20,22	24	Every 4 weeks
Inclusion/exclusion criteria	x	x					
Informed consent	x						
Demographic data		x					
History of ITP		x					
Other medical history		x					
Physical examination		x				x	
Bleeding score[1]		x	x	x	x	x	x
Haematology[2] (local lab)	x and Haptoglobin DAT		x	x	x	x	x
Blood sampling/biobank		week 0,4 and 16				x	
Platelet bound antibodies[9]		week 0 and 16				x	
Stool sampling		x					
Biochemistry[3] (local lab)		week 0 and 16				x	
Ig quantification (local lab)[4]		week 0 and 16				x	
Pregnancy test (relevant[5]		x	x	x	x	x	
bone marrow sampling[6]		week 0 and 16					
HiV/ hepatitis tests	x						
Red cells antibody screening (local lab)		x					
Quality of life and fatigue[7]		x			x	x	
Concomitant therapies	x	x	x	x	x	x	x
Other treatment of ITP	x	x	x	x	x	x	x
Daratumumab injection			x	x			
AE/SAE			x	x	x	x	x

Immunogenicity (ADA)[8]		Blood samples for ADA measurement will be taken at weeks 1,4,8,16,24

[1] World Health Organization Bleeding Assessment scale ± Khellaf bleeding score, [2] Haematology analyses: platelets, hemoglobin, Complete Blood Count with differential analysis. Two separate platelet counts measurements required at week 16 and 24(taken at least 24 hours but not longer than 7 days apart), [3] Blood analyses: LDH, ASAT, ALAT, bilirubin, creatinine, CRP, [4]IgG quantification must be taken at baseline, week 16, 24[5]Pregnancy tests must be taken at baseline and then every 4 weeks and until three months after the last daratumumab injection and at the end of study visit, [6] Study samples at Oslo University hospital OUS(week 0,4,16,24, only Norwegian and French centers) and biobanking (only Norwegian centers) at Ostfold Hospital Trust (week 0 and 24), [7] HRQoL and fatigue will be recorded at baseline, week 16 and 24 of follow up); [8]Blood sampling during treatment weeks should be taken before drug administration,(only Norwegian centers) [9]only Norwegian centers, *last visit (at week 24) for the last patient.

[**]Patients with no response will be followed only until study week 24. Participants with loss of response who require continued use of other ITP- directed therapies with be taken out of the study after week 24.

12.6 Protocol deviations

Centre	Patient code	Protocol deviation category	Description	Deviation classification (important yes/no)	Preventive action	Report to HA or EC
Østfold Hospital Trust Kalnes	NO-01-02	subject received wrong treatment or incorrect dose	valacyclovir prophylaxis not taken for 2 weeks after the last IMP inhection. Resumed after it was discovered.	yes	remind patient to adhere to all treatments, including concomitant medication in the study	no
		other	pregnancy during the follow up, >3 months after the last IMP dose.	no	none	NA
	NO-01-03	subjects entered study even though they met the exclusion criteria	pos HBcAb and HBsAb at screening	yes	received entecavir prophylaxis	no
Oslo University Hospital	NO-02-01	other	patient started treatment 2 weeks after screening (not able to come to clinic)	no	none	NA
	NO-02-03	other	treatment start 1 week later than scheduled in the protocol	no	none	NA
Akershus University Hospital	NO-03-02	other	treatment week 1 delayed for 2 days due to IMP not received on site at scheduled day.	no	none	NA
		failure to collect/measure platelet count during treatment or follow up period	patient did not come for follow up visit 11	no	none	NA
	NO-03-03	other (postponed treatment)	IMP dose 3 given 14 days after scheduled date due to SAE.	no	none	NA
	NO.03-04	other (GCP breach, study week 4)	visit performed by the doctor not in delegation list	no	none	NA
		Other (GCP breach, study week 22)	visit performed by the doctor not in delegation list	no	none	NA

NA, not applicable; HA, Health Authority; EC, Ethic Committee
HBcAb, Hepatitis B virus core antibody; HBsAb, Hepatitis B surface antibody

12.7 Bleeding assessment

			WHO bleeding scale*			Khellaf Bleeding Score**		
Patient	Response week 12/16	Response week 24	Baseline	Week 12/16	Week 24	Baseline	Week 12/16	Week
1	yes	yes	1	0	0	1	NA	NA
2	no	no	1	0	1	4	NA	4
3	yes	no	0	0	0	NA	NA	NA
4	yes	no	0	0	0	NA	NA	NA
5	yes	yes	0	0	0	NA	NA	NA
6	no	no	0	0	0	NA	NA	NA
7	yes	yes	0	0	0	NA	NA	NA
8	no	no	0	0	0	NA	NA	NA
9	yes	yes	0	0	0	NA	NA	NA
10	no	no	0	0	0	NA	NA	NA
11	no	no	1	1	1	7	9	7
12	no	yes	0	0	0	NA	NA	NA
13	no	no	1	0	0	2	NA	NA
14	no	no	0	0	0	NA	NA	NA
15	yes	yes	2	1	0	4	2	NA
16	no	no	1	0	0	2	NA	NA
17	yes	yes	1	0	0	NE	0	0
18	no	no	0	0	0	NA	NA	NA
19	yes	no	1	1	1	4	2	4
20	yes	yes	1	0	0	2	NA	NA
21	no	no	1	1	1	2	1	3

WHO bleeding scale, World Health Organization Bleeding score.

* WHO bleeding scale is graded from 0 to 4 (grade 0, no bleeding; grade 1, petechiae; grade 2, mild blood loss; grade 3, gross blood loss; grade 4, debilitating blood loss) according to verbal responses to questions and physical examination

† Khellaf bleeding score: bleeding severity is graded on a numerical scale based on physical examination. Khellaf bleeding score was assesses only in patients with WHO bleeding score of 1 or higher.

NE, not evaluated, NA, not applicab

12.8 Individual responses, efficacy endpoints

Treatment group	Patient	Sex (M/F)	Response (yes/no)*	Sustained response# (yes/no)	Duration of response§, days	Time to treatment failure†, days
Safety run-in	NO-01-01	M	no	no	n/a	n/a
	NO-01-02	F	yes	no	73	122
	NO-04-01	M	yes	yes	1010	1010
Cohort 1	NO-01-03	M	yes	yes	365	365
	NO-01-04	M	no	no	n/a	n/a
	NO-02-01	F	yes	yes	798	798
	NO-02-02	F	no	no	n/a	n/a
	NO-02-03	M	no	yes	568	568
	NO-03-01	F	yes	no	96	405
	NO-03-02	M	yes	yes	653	680
	NO-03-03	M	no	no	n/a	n/a
	NO-04-01	F	no	no	n/a	n/a
Cohort 2	NO-01-05	F	yes	no	35	35
	NO-02-04	M	no	no	n/a	n/a
	NO-03-04	M	no	no	n/a	n/a
	NO-04-03	M	no	no	n/a	n/a
	DK-01-01	M	yes	yes	351	351
	DK-01-02	M	no	no	n/a	n/a
	DK-01-03	M	yes	yes	260	260
	DK-01-04	F	yes	yes	232	232
	FR-01-01	M	no	no	n/a	n/a

*****Response (primary efficacy endpoint): platelet count $\geq 50x10^9$/L in 2 measurements (taken at least 24 hours apart) during week 12 for patients in safety run-in and cohort 1, and week 16 for patients in cohort 2, without having received rescue therapy for the last 4 weeks, nor having had dose increment of TPO-RA or corticosteroids during the study period

#Sustained response (secondary efficacy endpoint): platelet count $\geq 50x10^9$/L in 2 measurements (taken at least 24 hours apart) measured at study week 24 (+/-2 weeks) without having received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids.

§Duration of response: duration of sustained platelet count $\geq 50x10^9$/L without having received any platelet elevating therapy or having had dose increment of TPO-RA and/or corticosteroids. Duration will not consider the 4 weeks following the last daratumumab injection in the study. Loss of response is defined as platelet count $< 50 \times 10^9$/L after achieving response, in 2 consecutive blood samples taken at least 24 hours apart.

†Time to treatment failure: the time with platelet count $\geq 50x10^9$/L from 4 weeks after the last daratumumab injection to the first platelet count $<30x10^9$/L of two counts taken in two consecutive measurements at least 24 hours apart, or administration of any platelet elevating therapy after achieving response. Date of first platelet count measurement or administration of platelet elevation therapy will be used for the calculation of TTF.

n/a, nor applicable

12.9 Cumulative subject exposure

	Treatment	Number of subjects	Patients not treated	Cumulative exposure (in treated patients)
Safety run- in	Daratumumab 1800 mg weekly, 4 doses	3	0	3
Cohort 1	Daratumumab, 1800 mg weekly, 8 doses	9	0	12
Cohort 2	Daratumumab, 1800 mg weekly, 8 doses and 2 biweekly doses (total of 10 doses)	9	0	21

13 Attachments

1. Patient Consent Sample (Norway)
2. Study protocol and amendments
3. Statistical analysis plan (SAP v1.0)
4. List of signatures of investigators