
**Pierre Fabre Médicament, Les Cauquillous, 81500 Lavaur-France**

# Phase I/II Open Label Dose Escalation and Dose Expansion Study of Intravenous Infusion of W0101, an Antibody-drug Conjugate, in Patients With Advanced or Metastatic Solid Tumors. International, Multicenter, Open Label Study

**(W00101 IV 1 01)**

## 1 ABBREVIATED CLINICAL STUDY REPORT

**Date of version: 11 November 2022**

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| **EudraCT Number:** | 2017-001842-82 |
| **Name of Investigational Product:** | W0101 (lonigutamab ugodotin) |
| **Phase of Development:** | I/II |
| **Date of First Observation:** | 24 November 2017 |
| **Date of Last Observation:** | 04 October 2021 |
| **Study Termination Date:** | 05 July 2022 |
| **Indication Studied:** | Advanced or metastatic solid tumours |
| **Study Design:** | Open label dose escalation and dose expansion study in subjects with advanced or metastatic solid tumours |
| **Study Sponsor** | Pierre Fabre Médicament |
| **Sponsor's Contact:** | Dr. Eric Chetaille<br>Institut de Recherche Pierre Fabre<br>3, Avenue Hubert Curien<br>BP 13562-31035 Toulouse Cedex 01 |
| **Date of Report:** | **11 November 2022** |

This study was conducted in accordance with the International Council for Harmonisation tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents.

# 2 SYNOPSIS

<table>
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<tr><td colspan="3">Title of Study: Phase I/II open label dose escalation and dose expansion study of intravenous infusion of W0101, an antibody-drug conjugate, in patients with advanced or metastatic solid tumors.<br>International, multicenter, open label study (W00101 IV 1 01)</td></tr>
<tr><td colspan="3">Investigators:<br>This study was conducted under the direction of the following investigators:
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<tr><th>Investigator Name</th><th>Centre Number</th></tr>
<tr><td>Patricia Martin-Romano, MD (formerly Christophe Massard, MD)</td><td>FRA_0501</td></tr>
<tr><td>Carlos Gomez-Roca, MD</td><td>FRA_0502</td></tr>
<tr><td>Elena Garralda Cabanas, MD</td><td>ESP_1101</td></tr>
</table></td></tr>
<tr><td colspan="3">Study Centres: This study was conducted at 3 centres in 2 countries (2 centres in France, and 1 centre in Spain).</td></tr>
<tr><td colspan="3">Publication (Reference): None.</td></tr>
<tr><td colspan="2">Studied Period:<br>24 November 2017 (date of first subject observation)<br>04 October 2021 (date last subject completed study)</td><td>Phase of Development: I/II</td></tr>
<tr><td colspan="3">Primary Objectives:<br>This study was planned to be conducted in 2 phases. The primary objectives of each phase were:<br>• Phase I (Escalation Cohorts): To determine the maximum tolerated dose (MTD) and schedule and to characterise the dose-limiting toxicities (DLTs), after the administration of W0101, given as monotherapy intravenous (IV) infusion.<br>• Phase II (Expansion Cohorts): To evaluate the efficacy by objective response rate in subjects with specific tumour types showing insulin-like growth factor 1 receptor (IGF-1R) overexpression.<br>Secondary Objectives:<br>The secondary objectives of each phase were to:<br>Phase I (Escalation Cohorts):<br>• To evaluate the safety and tolerability of W0101<br>• To determine the recommended dose for expansion (RDE) cohorts<br>• To evaluate preliminary antitumour activity<br>• To characterise the pharmacokinetics (PK) of total antibody-drug conjugate (tADC), total monoclonal antibody (tmAb), cysteine-linker-cytotoxic entity (cysteine drug linker [F558565]), and naked cytotoxic drug (F554443)<br>• To describe the immunogenicity<br>Phase II (Expansion Cohorts):<br>• To evaluate the safety and tolerability profile<br>• To characterise the preliminary antitumour activity by evaluation of progression free survival [PFS] and duration of response in subjects with specific tumour types with an overexpression of IGF-1R.</td></tr>
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- To characterise the PK of tADC, tmAb, cysteine drug linker (F558565), and naked cytotoxic drug (F554443).
- To evaluate the immunogenicity.

**Exploratory Objectives**:

The exploratory objectives of each phase were to:

**Phase I (Escalation Cohorts)**:

- To determine the level of expression of IGF-1R by immunochemistry (IHC) in archival tumour samples of included subjects and correlate with clinical activity (Cohorts A1 and A2 only).
- To explore changes in IGF-1R expression in peripheral blood cells following treatment.
- To explore a potential link between circulating levels of IGF1, IGF1 binding protein, and clinical activity (Cohorts A1 and A2 only).
- To identify tumour genomic biomarkers in tumour samples or in circulating tumour DNA potentially linked to response or resistance to W0101.

For Cohort A3:

- To characterise the pharmacodynamic changes in the tumour associated with W0101 administration (in subjects providing on-treatment tumour biopsy).
- To correlate the level of IGF-1R expression on the primary and metastatic tumours.
- To characterise the clinical activity of W0101 in specific subject subgroups including but not restricted to:
  - Number and type of prior systemic therapies
  - PIK3CA and ESR1 mutation status

**Phase II (Expansion Cohorts)**:

- To determine the level of expression of IGF-1R by IHC in tumour samples of included subjects to correlate the level of expression at baseline to potential clinical activity.
- To identify tumour genomic biomarkers in tumour samples or in circulating tumour DNA potentially linked to response or resistance to W0101.
- To characterise pharmacodynamics based on the expression of IGF-1R by IHC in tumour samples in subjects with specific tumour types selected through high expression of IGF-1R.

**Methodology:** This was a phase I/II, multicentre, open label study divided into 2 parts: an initial dose escalation with dose findings (Phase I) followed by expansion cohorts (Phase II).

**Phase I (Dose Escalation)**

- Cohort A1: A 14-day treatment cycle cohort (Q2W administration schedule) with doses ranging from 0.07 mg/kg to possibly 5 mg/kg. At least 2 subjects were included at each dose level. Each subject was evaluated for DLTs during the first 2 cycles (including dose delays). The dose escalation proceeded using a design based on Bayesian logistic regression model (BLRM). An MTD/RDE1 was to be established first based on the BLRM supported dose toxicity relationship. Emerging PK and safety data were integrated within a PK and PK-pharmacodynamic model. This model was used to support decision-making in selecting doses and/or dosing schedule and transition to the second dose escalation

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Cohort A2. The late or cumulative toxicities period lasted from the end of the DLT period to the first dose administration in Cycle 5.

- Cohort A2: A 21-day treatment cycle cohort (Q3W administration schedule) with doses ranging from 0.30 mg/kg to possibly 5 mg/kg. For each dose level, at least 2 subjects, or a multiple of 2 subjects were to be included. The dose escalation proceeded using a design based on BLRM. Each subject was evaluated for DLTs from first administration (C1D1) to Day 8 after the second administration (C2D8). The MTD/RDE2 was to be established on the basis of the dose-toxicity relationship via BLRM modelling. The late or cumulative toxicities period lasted from the end of the DLT period to the first dose administration in Cycle 4.
- Specific MTDs were determined for Cohorts A1 and A2, and so the MTDs by cohort may have been the same or different.
- Cohort A3: A 28-day treatment cycle cohort (every 4 weeks administration schedule). This cohort was planned to investigate a new dose and schedule based on clinical and preliminary PK data generated from subjects included in Cohorts A1 and A2. All subjects were to start at a loading dose of 1.5 mg/kg followed by every 4 weeks maintenance dose of 1.2 mg/kg. The schedule was to be evaluated with at least 6 DLT-evaluable subjects using Bayesian posterior probability with continuous monitoring of toxicity. A Bayesian posterior probability of response rate was to be used to monitor the response rate for at least 12 subjects evaluable for efficacy. This cohort was to be restricted to breast cancer subjects with oestrogen receptor-positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) tumour that overexpressed IGF-1R, defined as ≥50% of tumour cells showing high membranous expression scored 3+ by IHC.

**Phase II (Dose Expansion)**

- It was anticipated to include around 4 expansion cohorts of subjects with specific advanced or metastatic cancer tumour types overexpressing IGF-1R. The selected dose and dosing regimen were planned to be chosen based upon the results emerging from Phase I part.

***Note: This study was terminated early due to the delay in subject recruitment in the Cohort A3 and investigational medicinal product manufacturing issues. No subjects were treated in Cohort A3, and Phase II was not conducted. All subjects from previous cohorts (Cohorts A1 and A2) completed the study.***

**Number of Subjects:**

**Planned**: Up to 380 subjects were to be included in the study (up to 100 subjects in Phase I and approximately 280 subjects in Phase II).

**Actual**: In Cohort A1, 26 subjects were screened, of whom 21 subjects were enrolled into the treatment assigned set (TAS). In Cohort A2, 23 subjects were screened, of whom 14 subjects were enrolled into the TAS.

**Diagnosis and Criteria for Inclusion:**

**Inclusion Criteria**:

1. Male or female subjects aged ≥18 years
2. Subjects with histologically or cytologically confirmed advanced or metastatic solid tumours (excluding lymphoma), unresponsive to standard treatment, or for whom no standard treatment was available or appropriate.
    i. In Cohort A1: Preferentially squamous non-small cell lung cancer, larynx carcinoma, ER positive breast cancer, and soft tissue sarcomas.

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ii. In Cohort A2:
   i. Squamous non-small cell lung cancer, squamous head and neck carcinoma and breast cancer (ER+, HER2-).
   ii. Others advanced solid tumour types with documented overexpression or genomic amplification of IGF-1R or that were deemed by the investigator to have a high probability of overexpressing IGF-1R.

3. Formalin-fixed paraffin-embedded archived tumour tissue block or representative slides for retrospective assessment of IGF-1R status after inclusion in the study.
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
5. Adequate bone marrow at screening
   *i. Absolute neutrophil count ≥1,500/mm$^3$.*
   *ii. Platelet count ≥150,000/mm$^3$.*
   *iii. Haemoglobin ≥9 g/dL (6.2 mmol/L)*
   *Note: Any blood product transfusion was prohibited within 2 weeks before the first study treatment administration (Cohorts A1 and A2 only).*
6. Adequate liver function at screening
   *i. Total bilirubin ≤ 1.5 mg/dL (≤26 µmol/L, SI unit equivalent)*
   *ii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 upper limit of normal (ULN), ULN ≤5 in case of liver metastasis*
   *iii. For subjects with Gilbert's syndrome: total bilirubin <2.5 ULN*
7. Adequate renal function at screening
   *Note: Serum creatinine ≤1.5 normal institutional limits or calculated (Cockroft-Gault) creatinine clearance ≥60 mL/min for subjects with creatinine levels above 1.5 normal institutional limits.*
8. Adequate electrolyte profile, defined as absence of clinically significant alterations requiring IV corrective measures.
   *Note: Subjects with electrolyte (calcium, potassium, and magnesium) alterations considered as not clinically significant as per the investigator assessment may have been eligible for the study.*
9. Subject must have recovered from all non-haematological toxicities from previous cancer therapies to at least Grade 1 (except alopecia).
10. Subject must have had measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 criteria.
11. Nonpregnant and adequate method of contraception for female subject of childbearing potential:
    In Cohorts A1 and A2 only:
    *i. Negative serum beta human chorionic gonadotropin test or negative urine pregnancy test within 72h prior to first study treatment administration.*
    *ii. Use of an effective method of contraception (hormonal contraception or intrauterine device) assessed by the investigator, for at least 2 months before the first study treatment administration, and agreement to go on using it during the whole duration of the study and up to 4 months after the last dose of the study treatment*

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*Note: a female subject of childbearing potential was a woman who was not permanently sterilised or not postmenopausal (postmenopausal is defined as 12 months with no menses without an alternative medical cause).*

12. In Cohorts A1 and A2 only: Adequate method of contraception for fertile male with a childbearing potential partner:

    *Note: Use of double barrier contraception method (use of condom for male and effective contraception method for the partner) from the entire duration of the study to 4 months after the last dose of the study treatment.*

    *Note: Please refer to the clinical study protocol in Appendix 16.1.1 for contraceptive guidance.*
13. Signed written informed consent before any screening procedure.
14. Affiliated or beneficiary of a social security system (if applicable in the national regulation).

**Exclusion Criteria:**

15. History of anti-cancer therapies within 4 weeks (or ≤5 half-lives for targeted agents) of initiating study treatment

    *Note: Anti-cancer therapies were defined as: major surgery, radiotherapy (palliative setting was allowed), hormonal therapy, immunotherapy, any conventional cytotoxic chemotherapy or other anti-cancer treatments. For cohorts A1 and A2 only, treatment with hormonal therapy for patients with breast or prostate cancer was allowed during the 4-week window.*
16. Known active or uncontrolled infections (bacterial, fungal, viral including Hepatitis B virus and Hepatitis C virus infections)
17. Symptomatic brain metastases, central nervous system tumors
18. Symptomatic motor or sensory peripheral neuropathy (≥ Grade 2) (cohorts A1 and A2 only)
19. Subjects having ophthalmologic abnormalities (cohorts A1 and A2 only)

    *Note: Ophthalmologic abnormalities were defined as subjects with monocular vision or having media opacities or any other condition that precludes monitoring of the retina or the fundus or having a history or current ophthalmology exam with retina or cornea abnormalities, especially central serous retinopathy, age related macular degeneration, retina degradation, corneal ulcers, cornea dystrophies or other pathology at the discretion of the ophthalmologist/investigator.*
20. Active serious systemic disease (infection, organic or dysmetabolic disease)
21. Subjects with uncontrolled high blood pressure

    *Note: systolic blood pressure >150 mmHg and/or diastolic blood pressure >95 mmHg despite treatment on 2 out of 3 determinations done in case that the first one meets the criterion for exclusion*
22. Subjects with Type 1 or 2 diabetes mellitus considered as poorly controlled according to the investigator's judgment.

    *Note (cohorts A1 and A2 only):*

    **i.** *Hb A1C ≥7%*

    **ii.** *Diabetes mellitus requiring insulin treatment*

    **iii.** *Diabetes mellitus with clinical signs*

    **iv.** *Fasting Plasma Glucose (FPG) ≥140 mg/dL / 7.8 mmol/L*
23. Serum albumin <30 g/L at screening
24. History of another malignancy

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*Note: (except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin, or any other curatively treated malignancy that had not been treated or recurred in the prior 3 years).*

25. Biologic therapy (eg, antibodies), including antibody-drug conjugates (ADCs): ≤4 weeks before first study treatment administration
26. Participation into a clinical study of an investigational agent within 4 weeks before the first study treatment administration.

    *Note: Subjects participating in the follow up period of previous studies (with no drug administration) may be eligible for the study*
27. Left ventricular ejection fraction (LVEF) <45% as determined by multigated acquisition scan or echography at screening
28. QTc > 470 msec on screening electrocardiogram or congenital long QT syndrome (cohorts A1 and A2 only)
29. Subjects who had any medical condition that would, in the investigator's judgment, prevented the subject's participation in the clinical study due to safety concerns or compliance with clinical study procedures.

    *Note: Any severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that might increase the risk associated with study participation or study treatment administration or that might interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for the study*
30. Prior anti IGF-1R therapy (cohorts A1 and A2 only)
31. Subject liable not to comply with protocol instructions in the investigator's opinion
32. Subject linguistically or mentally unable to understand the nature, objectives, and possible consequences of the trial, or refusing to subject himself/herself to its constraints
33. Subject family member or work associate (secretary, nurse, technician) of the investigator
34. Subject having forfeited his / her freedom by administrative or legal award or being under guardianship
35. Female subject pregnant or lactating
36. Known hypersensitivity to drug or metabolites of similar chemical classes

**Test Product, Dose, Mode of Administration, and Lot Numbers:**

**Test Product**: W0101 is an ADC combining a cytotoxic derivative from auristatin (an antimitotic agent which inhibits cell division by blocking the polymerisation of tubulin) to an anti-IGF-1R monoclonal antibody. The antibody moiety is considered as a vector that triggers a fast and strong internalisation of IGF-1R and internalises the cytotoxic drug within cells that overexpress IGF-1R. The auristatin derivative is released from the antibody by the lysosome and inhibits tubulin polymerisation, leading to cell death.

**Dose and Mode of Administration**:

**Phase I, Cohort A1**: W0101 was to be administered via a 1-hour IV infusion once Q2W to sequential dose level groups of at least 2 subjects, treated at ascending W0101 doses ranging from 0.07 mg/kg to 5 mg/kg.

**Phase I, Cohort A2**: W0101 was to be administered via a 1-hour IV infusion once every 3 weeks to sequential dose level groups of at least 2 or a multiple of 2 subjects, treated at ascending W0101 doses ranging from 0.30 mg/kg to 5 mg/kg.

**Lot Numbers**: PC20170902, PC20180308, PC20180601, PC20190207, PC20190603, PC20220204, and PC20200208

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**Duration of Treatment:** Until disease progression, occurrence of an unacceptable toxicity (occurrence of a toxicity that required a permanently study treatment discontinuation), subject refusal to continue investigational treatment, consent withdrawal, or subject lost to follow-up up to 12 months. Subjects showing continued clinical benefit may have continued treatment beyond 12 months after discussion with the Sponsor on a case-by-case basis.

A subject was considered to have completed the study if they completed all periods of the study including the safety follow-up (or efficacy follow-up whichever came last. If a subject discontinued treatment for one of the following reasons, the end of study participation was defined as the time point when subject discontinued treatment: withdrawal of consent, loss to follow-up, or death.

**Reference Therapy:** None.

**Criteria for Evaluation:**

**Safety**: Safety was assessed by monitoring and recording all adverse events (AEs) including DLTs, local laboratory tests, vital signs, ECOG performance status, physical examinations, ophthalmologic assessments, and local electrocardiograms. Laboratory testing included haematology, serum biochemistry, urinalysis, coagulation, and pregnancy testing as applicable.

**Efficacy (Antitumour Activity)**: Local tumour assessments using computed tomography scan or magnetic resonance imaging were performed from the first administration and were planned to occur every 6 weeks (Cohorts A1, A2). Activity was assessed by determining the objective response rate (complete response + partial response) as determined by Response Evaluation Criteria in Solid Tumours Version 1.1. The same method of evaluation (computed tomography or magnetic resonance imaging) performed at baseline should have been used at subsequent evaluation visits throughout the study.

**Pharmacokinetics**: The PK of W0101 were to be assessed using 3 assay methods to determine the circulating levels of tADC and tmAb using ligand binding assays; and F558565 (cysteine drug linker) and F554443 (naked cytotoxic drug) using an LC-MS/MS method. Additional exploratory investigations of potential degradation products or metabolites might have been performed if relevant using the same samples. These investigations may have been done in other matrices when available. PK parameters (eg, area under the plasma concentration versus time curve [AUC], $t_{1/2}$, maximum observed concentration, clearance [CL]) were assessed after the first 2 cycles.

Blood sampling:

*Phase I (escalation cohorts):*

Cohort A1

At total of 20 blood samples:

Cycle 1: T0 (predose), at the end of the infusion, T4h, T8h, T24h (Day 2), T72h (Day4), T168h (Day 8)

Cycle 2: T0 (predose = T336 hours Cycle 1), at the end of the infusion, T4h, T8h, T24h (Day2), T72h (Day 4), T168h (Day 8)

Cycle 3: T0 (predose = T336 hours Cycle 2), at the end of the infusion, T24h (Day 2)

Cycle 4: T0 (predose = T336 hours Cycle 3), at the end of the infusion, T24h (Day 2)

Cohort A2

At total of 18 blood samples:

Cycle 1: T0 (predose), at the end of the infusion, T6h, T24h (Day2), T72h (Day4), T168h (Day 8), T336h (Day 15)

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Cycle 2: T0 (predose = T504 hours Cycle 1), at the end of the infusion, T6h, T24h (Day 2), T72h (Day 4), T168h (Day 8), T336h (Day 15)

Cycle 3: T0 (predose = T504 hours Cycle 2), at the end of the infusion

Cycle 4: T0 (predose = T504 hours Cycle 3), at the end of the infusion

**From Cycle 5 to Safety Follow-up visit: T0 (predose) for tADC and human antihuman antibodies (HAHA) only.**

**Exploratory Biomarkers and Pharmacodynamics**:

**Phase I***:*

- IGF-1R expression in baseline tumour sample evaluated by IHC.
- Assessment of tumour mutational status in baseline tumour sample.
- Assessment of circulating IGF1 and IGF1BP in plasma at baseline and during treatment potentially linked to a pharmacodynamic effect (Cohorts A1 and A2 only).
- Assessment of IGF-1R expression in blood cells at baseline and during treatment potentially linked to a pharmacodynamic effect (surrogate pharmacodynamics).
- Assessment of cancer-linked mutations (including but not limited to ESR1 and PIK3CA mutations) in circulating tumour DNA.
- In Cohorts A1 and A2, ctDNA was be assessed at baseline and during treatment.

**Immunogenicity**: Immunogenicity testing to determine the presence of HAHA was undertaken before each W0101 administration. The last sample for immunogenicity assessment was taken at the safety follow-up visit. A 3-tier ligand binding assay was used to detect, confirm, and determine the titre of HAHAs. The proportion of subjects who became positive in this assay were reported.

**Statistical Methods:**

**Analysis Populations**:

- **Screened Set**: All subjects who signed an informed consent.
- **TAS**: All screened subjects assigned to treatment.
- **Full Analysis Set (FAS)**: All subjects from the TAS who received at least 1 dose of W0101.
- **Safety Analysis Set (SAF)**: All subjects who received at least 1 dose of W0101 and had at least one valid postbaseline safety assessment.
- **Dose-Determining Set (DDS)**: All subjects from the safety set who either met the minimum exposure criterion and had scheduled safety evaluations or discontinued earlier due to DLT.
- **Pharmacokinetics Set (PK)**: All subjects from the TAS who had at least 1 blood sample providing evaluable PK data.
- **Efficacy Set**: All subjects from the TAS who received at least 1 dose of W0101, with measurable disease at baseline and with an opportunity of being followed up for at least 1 valid postbaseline tumour assessment.

**Safety and Efficacy Analyses**

Phase I (Cohorts A1 and A2): Analyses of safety and antitumour activity were planned to be descriptive and presented by dose, as appropriate. Subject listings were also to be provided. The main objective of Phase I part was to determine the MTD and RDE. The MTD was the highest dose associated with DLT occurring during the DLT window in 30% of subjects. In Cohorts A1 and A2, a dose toxicity modelling based on BLRM was fitted all along

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the escalation-dose period. The dose toxicity relationships established via this model were used to support the decision-making in the dose selection process.

In case that a late or cumulative toxicity occurred in a subject, that subject was regarded as having an event similar to a DLT in the subsequent analyses aimed at selecting the doses. After each dose level group was included, the Safety Monitoring Board reviewed the safety data to determine whether to proceed with the next planned dose level. Clinical activity was evaluated as secondary objective.

**Pharmacokinetics**:

**Phase I**: Descriptive statistics on serum concentrations and PK parameters of tADC, tmAb, cysteine drug linker (F558565), and naked cytotoxic drug (F554443) (arithmetic mean, standard deviation, CV, geometric mean, geometric CV, median, [minimum – maximum]). Exploratory investigations of potential degradation products or metabolites could have been performed if relevant in other matrices when available.

**Sample Size**:

**Phase I**: A total of 35 DLT-evaluable subjects were included in the dose escalation cohort (21 subjects in Cohort A1 and 14 subjects in Cohort A2) to determine the MTD/RDE by administration cycle duration. These sample sizes provided satisfying probabilities of selecting the true MTD in the different scenarios investigated using BLRM modelling. Any nonevaluable subject was replaced.

## SUMMARY OF RESULTS

**Study Subjects:**

In Cohort A1, a total of 26 subjects were screened, of whom 21 (80.8%) subjects were enrolled. Four (15.4%) subjects were screen failures. One (3.8%) subject was not assigned the study treatment because of an AE. In Cohort A2, a total of 23 subjects were screened, of whom, 14 (60.9%) subjects were enrolled. Eight (34.8%) subjects were screen failures. One (4.3%) subject withdrew consent prior to starting study treatment. The majority of subjects in both cohorts were aged <65 years (in the 18 to 64 years age category) (median age: Cohort A1, 54 years; Cohort A2, 62 years), White, and non-Hispanic or Latino. The predominance of females was seen in Cohort A1 (~3:1), whilst there was a similar proportion of females and males in Cohort A2. In addition, all subjects in Cohort A1 and A2 had an ECOG performance status of 0 or 1. Most subjects in both cohorts presented with Stage IV disease. In both cohorts, breast cancer was the primary tumour type most frequently reported. Positivity for IGF-1R was reported in 5 (23.8%) subjects in Cohort A1 and in 9 (64.3%) subjects in Cohort A2. The subjects received the cumulative median dose of 2.40 mg/kg (range: 0.3 to 8.4 mg/kg) in Cohort A1 and 2.20 mg/kg (range: 1.2 to 12.0 mg/kg) in Cohort A2.

**Safety Results:**

- In Cohort A1 (N= 21),
  - One single DLT was observed in each of the 1.05 mg/kg, 1.2 mg/kg and 1.5 mg/kg dose group and 2 DLTs were observed in the 2.4 mg/kg dose group. In the 1.05 mg/kg dose group the DLT was a late or cumulative toxicity at Cycle 3; other DLTs occurred during the DLT reporting period. All but one DLTs were ≥ Grade 3 thrombocytopenia lasting > 7 days or grade ≥ 2 associated with bleeding. A DLT of AST or ALT Grade 4 or AST or ALT Grade 3 for ≥ 7 consecutive days occurred in the 1.2 mg/kg dose group. The median posterior probability of DLT occurrence was 29.8% (95% CrI 11.57-57.28) for the 1.20 mg/kg dose level. Therefore, the BLRM model recommended the dose of 1.20 mg/kg as MTD for Cohort A1.

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- All (100%) subjects experienced at least 1 treatment-emergent AE (TEAE) with 19 (90.5%) subjects reporting TEAEs related to the study drug. Overall, the most commonly (≥15%) reported TEAEs (all grades, regardless of relationship to study treatment) were thrombocytopenia (66.7%), AST increased (57.1%), fatigue (38.1%), ALT increased (33.3%), constipation (28.6%), neutropenia and pyrexia (both 23.8%), blood creatine phosphokinase increased, nausea, arthralgia, and headache (all 19%).
  Twelve (57.1%) subjects reported National Cancer Institute (NCI) common terminology criteria for AEs (CTCAE) grade ≥3 TEAEs, of whom 8 (38.1%) subjects reported TEAEs related to the study drug (at dose levels of 1.05 mg/kg and above). The most commonly (≥10%) reported Grade 3 or 4 TEAEs were thrombocytopenia (14.3% and 19.0%, respectively) and Grade 3 AST increased (19%).
- One (4.8%) subject (1.2 mg/kg dose group) reported TEAEs (tumour pain [Grade 3]), starvation [Grade 2], and general physical health deterioration [Grade 5] - all not related to study treatment) leading to the study drug being withdrawn. Five (23.8%) subjects reported TEAEs leading to study drug interruption. Interruptions occurred in 2 subjects each in the 1.2 mg/kg and 1.5 mg/kg dose groups and in 1 subject in the 2.4 mg/kg dose group. TEAEs of thrombocytopenia was responsible for interruption in all subjects; in addition, limb asymmetry and gamma-glutamyltransferase (GGT) increase led to dose interruption in 1 subject in the 1.2 mg/kg subgroup and AST increased in 1 subject in the 1.5 mg/kg subgroup.

- In Cohort A2 (N=14),
  - Two subjects reported at least 1 DLT occurring during the DLT period and/or the late or cumulative toxicity period. A DLT occurring in the 1.05 mg/kg group was a late or cumulative toxicity at Cycle 3 and a DLT in the 1.2 mg/kg group occurred during the DLT period. Both DLTs were ≥ Grade 3 thrombocytopenia lasting >7 days or grade ≥2 associated with bleeding. The BLRM model recommended the dose of 1.37 mg/kg (80% CrI 0.06-10.0) as MTD. The 80% CrI for the MTD was large due to the limited sample size and the high uncertainty defined in the prior distribution of the model. The 1.20 mg/kg dose level was the nearest lower tested dose level compared to MTD. The median posterior probability of DLT occurrence was 17.4% (95% CrI 2.63-48.39).
  - All (100%) subjects experienced at least 1 TEAE, with 11 (78.6%) subjects reporting TEAEs related to the study drug. The most commonly (≥15%) reported TEAEs were thrombocytopenia (78.6%), AST increased (42.9%), asthenia (35.7%), ALT increased and dyspnoea (both 28.6%), fatigue, epistaxis, pleural effusion, and proteinuria (all 21.4%). Nine (64.3%) subjects reported NCI CTCAE grade ≥3 TEAEs, of whom 5 (35.7%) subjects reported TEAEs related to the study drug. The most commonly (≥10%) reported Grade 3 or 4 TEAEs were thrombocytopenia (21.4% and 14.3%, respectively), AST increased (14.3% [Grade 3]), and GGT increased (14.3% [Grade 3]).
  - One (7.1%) subject reported a TEAE leading to drug interruption (1.1 mg/kg dose group, proteinuria (Grade 3). No TEAE led to study treatment withdrawal.

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- In Cohort A1 (N=21), 8 (38.1%) subjects experienced at least 1 serious TEAE, whilst in Cohort A2 (N=14), 6 (42.9%) subjects experienced at least 1 serious TEAE. The serious TEAE observed in at least 2 subjects across the 2 cohorts were thrombocytopenia (in 1 subject each from the 1.2 and the 1.5 mg/kg dose groups, in 2 subjects from the 2.4 mg/kg dose group in Cohort A1 and in 1 subject each from the 1.05 and the 1.2 mg/kg dose groups in Cohort A2) and general physical health deterioration in 1 subject in each cohort. Thrombocytopenia was the only serious TEAE reported as related to study treatment.
- Overall, 3 deaths were reported: 1 in Cohort A1 (due to general physical health deterioration) and 2 in Cohort A2 (due to general physical health deterioration and dyspnoea); all were related to the progression of the underlying cancer.
- Changes in haematological and biochemistry parameters correlated with the reported TEAEs of thrombocytopenia and hepatic enzymes abnormalities No other remarkable changes were observed.

**Efficacy Results:**

In Cohort A1, of the 20 total subjects in the efficacy population, 4 (20%) subjects reported stable disease (SD) as their best response, and 16 (80%) subjects reported progressive disease as their best overall response. Similarly, in Cohort A2, of 14 total subjects, 2 (14.3%) subjects reported SD as their best response, and 11 (78.6%) subjects had progressive disease as their best overall response. There was no objective response (partial response or complete response) in IGF-1R-positive subjects (5 subjects for Cohort 1 and 9 subjects for Cohort A2).

**Pharmacokinetic Results:**

For both Cohorts A1 (Q2W dosing regimen) and A2 (every 3 weeks dosing regimen), no measurable concentrations were observed for F554443 with all concentrations (below the limit of quantification [BLQ]) at all DLs (<0.01 ng/mL or 0.0116 nmol/L).

For F558565, no measurable concentrations were observed from 0.07 mg/kg to 0.6 mg/kg (first 4 dose levels) with concentrations (BLQ) (<0.1 ng/mL or <0.0848 nmol/L). From 1.2 mg/kg onwards, mean serum concentration profiles were flat with no major burst effect and measurable concentrations not exceeding 0.4 nmol/L (0.47 ng/mL). Therefore, F558565 levels represent a very small proportion compared to the circulating levels of W0101 (2- to 4-log difference).

tmAb and tADC PK profiles presented a similar shape across all studied dose levels independent of the dose regimen. Terminal elimination phases increased with doses from 0.07 mg/kg to 0.3 mg/kg and then tended to start being parallel from 0.6 mg/kg up to 2.4 mg/kg. No major difference was observed between concentration PK profiles between cycles (Cycle 2 versus Cycle 1) at all tested dose levels and for both frequencies of administration.

Since minimal to no differences were observed in PK behaviour of tADC and tmAb based on the concentrations results, the discussions and conclusions in the following section will be based on tADC data only.

The median time of maximum serum peak level of tADC was generally observed at the end of the IV infusion (between 1 and 2 hours) for all tested dose levels and for both frequencies of administration.

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High intersubject variability was observed in AUC, for the first 4 dose levels (0.07 mg/kg, 0.15 mg/kg, 0.3 mg/kg, and 0.6 mg/kg), with CV% ranging from 57% to 102%. Low to moderate intersubject variability in AUC was observed for the higher doses (1.05 to 2.4 mg/kg), with CV% between 5% and 53%.

The exposure ratios of tADC area under the plasma concentration-time curve from zero to the last quantifiable point ($AUC_{0-t}$)/tmAb $AUC_{0-t}$ ranged from 0.512 to 1.52 across all dose levels and independent of dose regimen, indicating weak cytotoxic deconjugation.

Clearance decreased with increasing doses (from 0.07 mg/kg to 2.4 mg/kg for Cohort A1 and from 1.05 mg/kg to 1.20 mg/kg for Cohort A2) with clearance ranging from 0.303 mL/h to 6.12 mL/h.

For Cohort A1, individual estimated half-lives ranged from 14.2 hours to 92.4 hours for dose levels of 0.07 mg/kg to 0.6 mg/kg, and from 68.5 hours to 174 hours for dose levels of 1.05 to 2.4 mg/kg. For Cohort A2, individual estimated half-lives ranged from 31.6 hours to 189 hours for dose levels of 1.05 mg/kg to 1.2 mg/kg.

Considering the power model analyses and based on the slopes obtained by regression analysis for tADC, the PK exposure ($AUC_{0-t}$, $AUC_{0-inf}$, maximum observed concentration [$C_{max}$], and trough concentration [$C_{trough}$]) generally increased in a greater than dose proportional manner within the studied dose levels independent of the frequencies of administration.

No clear conclusion could be drawn from the repeated measures analyses on $C_{trough}$ observed after Dose 1 through the last dose compared with the average trough levels for the rest of the period to determine the time at which steady-state was achieved.

**Immunogenicity Results:**

Eighteen (18) serum samples were positive during a screening assay for anti-W0101 antibodies out of a total of approximately 136 samples collected and analysed. Four (4) serum samples out of these 18 were confirmed as positive during a confirmatory assay with titres between 5 and 10 during a titration assay.

The incidence of immunogenicity for W0101 was low (4 subjects were HAHA-positive independently of dosing regimen and dose level out of a total of 36 subjects). For Subject 0502046 and Subject 1101059, who were HAHA positive on cycle 2 predose, there is no impact on their PK parameters on cycle 1. However, they seem to be within the lower range of exposure on cycle 2 of the corresponding dose level. For subject # 1101027, who was HAHA positive on cycle 9 predose, there is no impact on $C_{trough}$ at Cycle 8, but $C_{trough}$ on Cycle 9 is the lowest of its own $C_{trough}$.

**Conclusions:**

- For the every 2 week schedule of administration (Cohort A1), the BLRM model recommended the dose of 1.20 mg/kg (95% CrI 11.57 57.28) as MTD. For the every 3 week schedule of administration (Cohort A2), the BLRM model recommended the dose of 1.37 mg/kg (80% CrI 0.06-10.0) as MTD.
- Overall, W0101 had a manageable safety profile for dose levels at or below 1.20 mg/kg for the every 2 week schedule of administration and at or below 1.37 mg/kg for the every 3 week schedule of administration.

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- The most frequently reported TEAE with both schedules of administration was thrombocytopenia, which was more frequent and most frequently reported as Grade ≥3 at the higher dose-levels and was also reported as DLT. Increased transaminases were also reported in ≥ 10% of subjects for both administration schedules and 1 DLT of AST or ALT Grade 4 or AST or ALT Grade 3 for ≥ 7 consecutive days was reported with the every 2 week schedule of administration.
- tmAb and tADC PK profiles were similar in shape and levels, with tADC/tmAb exposure ratio close to 1, suggesting good stability of the ADC construct in humans and a very limited release of cytotoxic drug.
- No major accumulation of either tmAb or tADC between cycles (Cycle 2 vs Cycle 1) was observed at all tested dose levels and for both regimens.
- The general PK behaviour of W0101 described a Target Mediated Drug Disposition, resulting in a decreased clearance with increasing doses between 0.07 to 1.05 mg/kg with a mean half-life of around 100 hours, leading to stable clearance.
- PK profiles of F558565 observed in the current study were indicative of a slow cleavage from ADC without any burst effect.
- The incidence of immunogenicity for W0101 was low (4 subjects were HAHA-positive independent of dosing regimen and dose level). HAHA positive subjects, at the cycle they were positive, displayed concentration and PK parameters within the lowest range.
- No responses were observed in either cohort, but SD was reported in 4 out of 20 evaluable subjects in the every 2 week schedule and 2 of 14 evaluable subjects in the every 3 week schedule of administration. No response was observed in subjects positive for IGF-1R.
- The exploratory results will be provided in a separate report.

**Date of Report:** 11 November 2022