2. SYNOPSIS

Name of Sponsor: Institut de Recherches Internationales Servier (I.R.I.S.)	*(For National Authority Use only)*
Name of Finished Product: Not applicable. **Name of Active Ingredient:** S95012 (also known as PRS-344/S095012)	

Title of Study: A first in human Phase 1/2 open-label, multicenter, dose escalation and expansion study of PRS-344/S095012 in participants with solid tumors

Protocol No.: CL1-95012-001

EudraCT: 2019-003456-36

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Coordinating Investigator:

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Number of Study Centers and Countries:

Overall, 4 countries and 11 centers were involved and 46 participants were enrolled. In Australia, 3 centers enrolled 9 participants; in Belgium, 3 centers enrolled 9 participants; in Spain, 3 centers enrolled 26 participants; in the United States, 2 centers enrolled 2 participants.

Studied Period:

Initiation date: 27 Sep 2021 (first informed consent form signed by first participant)

Completion date: 01 Apr 2025 (last visit last participant)

Phase of Development of the Study:

Phase 1/2

Publication (Reference):

Not applicable.

Background and Rationale for the Study:

PRS-344/S095012 is a monoclonal antibody (mAb)-like bispecific protein targeting the programmed death-ligand 1 (PD-L1), and the immune receptor 4-1BB. PRS-344/S095012 is constituted by the genetic fusion of a backbone-engineered anti-PD-L1 antibody and an agonistic 4-1BB-targeting moiety. Antitumor activity of S095012/PRS-344 combines both the checkpoint inhibition via the programmed cell death protein (PD-1)/PD-L1 axis and the activation of the 4-1BB mediated anticancer effect to provide a potent costimulatory signal to tumor antigen-specific T cells.

Current treatments for advanced and/or metastatic solid tumors include chemotherapies, targeted therapies, and immune checkpoint inhibitors. Despite their widespread use, these treatments are often limited by factors such as resistance, adverse effects, and suboptimal efficacy in certain patient populations. As a result, there is a critical need for new, more effective therapies that can offer more durable responses in these patients. PRS-344/S095012, with its unique mechanism of action, represents a potential new therapeutic option in this context. The intended mechanism of action of PRS-344/S095012, involving simultaneous PD-1/PD-L1 axis inhibition and PD-L1 dependent 4-1BB activation, showed promising results in preclinical models.

This first in human (FIH) Phase 1/2, multicenter, open-label, dose escalation and dose expansion study was designed to determine the safety and activity of PRS-344/S095012 in patients with advanced and/or metastatic solid tumors. Phase 1 assessed PRS-344/S095012 in participants for whom standard treatment options were not available, no longer effective, or not tolerated, while Phase 2 was planned to evaluate the potential efficacy in participants with cervical cancer (checkpoint inhibitor [CPI] naïve and CPI-relapsed/refractory) or cervical squamous cell carcinoma (CSCC). Per protocol amendment No. 8, dated 21 Aug 2023, obinutuzumab was planned to be administered as a means of preventing anti-drug antibody (ADA) formation in 1 cohort administered 14 to 7 days before the first dose of PRS-344/S095012.

Due to increased seriousness of liver toxicity observed when PRS-344/S095012 was combined with obinutuzumab and based on the overall safety and efficacy data, the Sponsor determined the overall benefit-risk balance of PRS-344/S095012 was unfavorable. Thus, recruitment into Phase 1 of the study was stopped on 04 Jun 2024.

Since the study was terminated during Phase 1, the Phase 2 part of the study was not initiated. An abbreviated clinical study report has been prepared to provide complete safety outcomes.

The most common (reported in ≥ 20% of participants) treatment-related adverse events (AEs) were fatigue, aspartate aminotransferase increased, alanine aminotransferase increased, infusion related reaction, cytokine release syndrome. During this study, an ongoing assessment of the risks of treatment with periodic evaluation of safety data was planned. The study was planned to be discontinued in the event of any (new) finding indicating a risk that would render continuation of the study unjustifiable.

Objective(s) and Endpoint(s):

Phase 1 Study Objectives	**Phase 1 Study Endpoints**
Primary	
• To evaluate the safety and tolerability profile of single-agent PRS-344/S095012	• Incidence of dose-limiting toxicities (DLTs) • Incidence and severity of AEs • Discontinuation of study treatment due to an AE • Laboratory, electrocardiogram (ECG) and vital sign measurements
• To determine the maximum tolerated dose (MTD) or maximum administered dose and recommended Phase 2 dose (RP2D) of PRS-344/S095012	• Incidence of DLTs

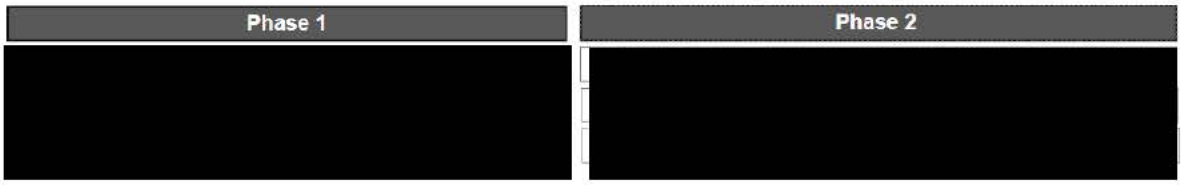
Phase 1 Study Objectives	**Phase 1 Study Endpoints**
Secondary	
• To characterize the pharmacokinetics (PK) of PRS-344/S095012	• Serum PK parameters of PRS-344/S095012
• To evaluate the immunogenicity of PRS-344/S095012	• Detection of ADA against PRS-344/S095012 and their titration when applicable
• To assess the preliminary antitumor activity of PRS-344/S095012 as per the investigator, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	• Objective Response (OR): Defined as Complete Response (CR) plus Partial Response (PR) • Duration of Response (DoR): defined as the time from first demonstration of response to progression or death, whichever occurs first • Progression-free Survival (PFS): Defined as the time from the first dose of treatment to first documented disease progression or death due to any cause, whichever occurs first • Overall Survival (OS): Defined as the time from first dose of study drug to death due to any cause

Phase 2 Study Objectives	**Phase 2 Study Endpoints**
Primary	
• To evaluate the potential antitumor activity and efficacy of PRS-344/S095012, as per central assessment according to RECIST v1.1 criteria based on appropriate clinical standards for the specified tumor type	• Arms 1 and 2: OR as per central assessment according to RECIST v1.1 criteria • Arm 3: OR as per central assessment and composite response criteria (digital medical photography and/or imaging as per RECIST v1.1)
Secondary	
• To further describe the efficacy	• All arms: – OR as per investigator assessment – Disease Control (DC) – DoR – PFS – OS – Time to Response
• To further characterize the safety and tolerability of PRS-344/S095012	• AEs, serious AEs • Laboratory, ECG, vital signs
• To further characterize the PK profile of PRS-344/S095012.	• Serum concentrations of PRS-344/S095012.
• To further characterize immunogenicity of PRS-344/S095012	• Detection of ADA against PRS-344/S095012 and their titration when applicable

Study Design:

The study was a FIH, Phase 1/2, multicenter, open-label, dose escalation and dose expansion study designed to determine the safety and activity of PRS-344/S095012 in participants with locally advanced and/or metastatic solid tumors.

The study was planned in 2 phases (Phase 1 and Phase 2); however, participants were only enrolled into Phase 1 due to the early termination of the study. The study plan for Phase 1 and Phase 2 is presented in the following figure:



Abbreviations: C = Cohort; CPI = checkpoint inhibitors, CSCC = cutaneous squamous cell carcinoma.
Dose levels were provisional and depended on the Bayesian Logistic Regression Model recommendation and cumulative safety data observed.

Phase 1 was planned to evaluate the safety and tolerability of PRS-344/S095012 in participants for which standard treatment options were not available, no longer effective, or not tolerated. In Phase 1, backfilling was planned to be allowed (i.e., the possibility for additional participants to receive study treatment at a dose level that had demonstrated an acceptable safety profile). The RP2D was to be determined based on safety, PK and pharmacodynamic data observed during Phase 1.

Phase 2 was planned to evaluate the potential efficacy of PRS-344/S095012 in 3 disease-specific expansion arms:

- **Arm 1 (Cervical CPI-naïve):** participants with recurrent, persistent and/or metastatic cervical cancer, who had not been previously treated with a CPI, and whose disease had progressed on any prior line of treatment.
- **Arm 2 (Cervical Cancer – CPI-relapsed/refractory)**: participants with recurrent, persistent and/or metastatic cervical cancer, who had received and progressed on any line of a CPI as monotherapy or in combination.

  Note: for cervical cancer in Arms 1 and 2, acceptable histologies were squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma; sarcomas and neuro-endocrine carcinomas were not eligible.
- **Arm 3 (CSCC – CPI-relapsed/refractory):** participants with advanced or metastatic CSCC who had received and progressed on CPI treatment.

This study was performed strictly in accordance with Good Clinical Practice.

Number of Participants (Planned and Analyzed):

Planned:

The number of participants was planned to be determined by the number of dose cohorts enrolled before reaching the MTD. It was expected that approximately 45 participants would be enrolled. Thirty additional participants were planned to be enrolled, if needed, to backfill cohorts.

In addition, approximately 10-12 participants were planned to be treated with PRS-344/S095012 preceded by obinutuzumab administration, with the objective of having safety, PK, pharmacodynamic, and ADA data over 2 cycles of treatment for 5-6 participants. The sample size was driven by having reasonable Wilson score intervals (at 80% confidence level) so that the following conclusions could be made when the target ADA prevention rate is 80%.

Scenario	Conclusion
No participants developed ADA	Target achieved.
1 participant developed ADA	Enroll additional participants to decide.
≥ 2 participants developed ADA	Target missed.

Due to the early termination of the study for safety reasons, participants were enrolled only in Phase 1.

Analyzed:

A total of 46 participants were enrolled in the study. Of them, 4 participants were enrolled in the PRS-344/S095012 12 mg group, 9 in the PRS-344/S095012 36 mg group, 14 in the PRS-344/S095012 60 mg group, 6 in the PRS-344/S095012 80 mg group, and 13 in the obinutuzumab + PRS-344/S095012 36 mg group.

- 45 (97.8%) participants were analyzed in the Treated Set (TS).
- 42 (91.3%) participants were analyzed in the Response Evaluable Set (RES).
- 36 (78.3%) participants were analyzed in the Dose-Limiting Toxicities Evaluable Set (DLTES).
- 44 (95.7%) participants were analyzed in the Pharmacokinetic Set (PKS).
- 39 (84.8%) participants were analyzed in the Immunogenicity Set (IGS).

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main inclusion and exclusion criteria are presented in this synopsis.

Participants ≥ 18 years of age, with:

- Documented disease progression on prior therapy before entry into the study.
- Eastern Cooperative Oncology Group performance status of 0 or 1.
- Royal Marsden Prognosis Score of 0 to 1.
- A life expectancy of at least 3 months following first investigational medicinal product (IMP) administration.
- Adequate organ function as assessed by laboratory tests within 7 days prior to pretreatment with obinutuzumab.
- Participants must have at least one measurable target lesion as per RECIST v1.1.
- Participants with no available archived material must have had 1 or more tumor lesions amenable to biopsy.
- Primary central nervous system malignancies and participants with Child-Pugh Class B8 or higher or C liver cirrhosis were excluded.
- Participants must not have had an active autoimmune disease or immune-related AEs currently requiring systemic anti-inflammatory agent > 10 mg/day prednisone or equivalent. Serologic testing for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) had to show absence of immunoglobulin M antibodies against CMV and EBV-Viral Capsid Antigen according to local standards.
- Prior history of Grade ≥ 3 immune-related pneumonitis, colitis, hepatitis, or myocarditis were also excluded.

Investigational Medicinal Product/Test Drug:

PRS-344/S095012 drug product is a concentrate for solution for infusion in a US Pharmacopeia and European Pharmacopeia Type I glass vial configuration (FluroTech® stopper and aluminum crimp). It was supplied in 20 mL vials with a nominal fill volume of 16 mL of product at a concentration of 25 mg/mL for IV administration. Each vial for administration contains 400 mg of PRS-344/S095012. For dosing, the required volume of product was diluted in saline with Polysorbate 80 (PS80) as a solvent (0.03% to 0.04% final concentration).

Treatment Dose of PRS-344/S095012: PRS-344/S095012 was to be administered as intravenous infusion every 2 weeks (q2w schedule), with at least 12 days between 2 infusions. In this schedule, participants were to receive PRS-344/S095012 on Day 1 and Day 15 of each 28-day cycle. The starting dose of PRS-344/S095012 was to be a 12 mg flat, with a maximum dose of 1,000 mg.

Obinutuzumab Drug Product was administered as a pretreatment. It was supplied as a 50 mL single dose glass vial containing 1000 mg liquid concentrate in 40 mL (25 mg/mL) for infusion. In addition to the drug substance, the solution also contained histidine/histidine-HCl, trehalose dihydrate and poloxamer 188. Obinutuzumab was to be administered either as a single dose of 2000 mg or 2 doses of 1000 mg on 2 consecutive days, as per the investigator's judgment. Within the first option, obinutuzumab was to be administered at the earliest 14 days (D-14) before the first dose of PRS-344/S095012 (Cycle 1 Day 1 [C1D1]), and at the latest, 7 days (D-7) before C1D1. If obinutuzumab was administered over two consecutive days, it was to be done at the earliest on D-14 and D-13 and at the latest on D-8 and D-7 before C1D1.

Comparator:

Not applicable.

Duration of Treatment:

For all participants, the study included:

A ***Screening Period***: a maximum of 3 weeks to check participants' eligibility criteria.

A ***Treatment Period***: at least 1 treatment cycle (initially consisting of 28 days), which corresponded to the DLT observation period in Phase 1. Participants were planned to be allocated to different dose levels in dedicated cohorts in Phase 1 or to dedicated arms in Phase 2 and receive doses of PRS-344/S095012 administered by IV infusion on Day 1 and Day 15 of each cycle, (i.e., q2w). After Cycle 1, in case of acceptable safety/tolerability profile, participants received additional cycles of PRS-344/S095012 until 1 of the following criteria applied:

- Confirmed radiographic/photographic disease progression.
- Unacceptable AEs according to investigator's judgment (including intervening illness that prevents further administration of treatment).
- Significant participant noncompliance with the protocol.
- Participant decision to withdraw from the treatment or study.
- Pregnancy.
- Investigator decision to withdraw the participant from the treatment or study.
- Participant was lost to follow-up (FU).
- Death.
- Sponsor decision to end the study early.
- 1 year from CR and 2 years for participants with PR (although treatment may have continued if benefits were expected to outweigh risks in consultation with Sponsor)
- Any other protocol deviation that resulted in a significant risk to the participant's safety.

End of treatment corresponded to the 3-month safety FU visit as described below.

A ***Follow-up Period*** which included:

- 1-month Safety FU visits: participants were to be evaluated 30 days after the last IMP administration.
- Long-term Safety FU visits: participants were to be evaluated 60 and 90 days after the last IMP administration
- Disease Status and Survival FU visits: disease status and survival were to be followed every 12 weeks (± 14 days)

The ***End of the study*** was defined as the data of the last FU of the last participant, which included the long-term safety FU visit, 90 days after the last dose of IMP, or the date of the last contact attempt if the last participant as declared lost to FU.

Statistical Methodology:
Participants were analyzed according to the actual treatment they received.

Analysis Sets:

- ES: All screened participants who were eligible to take part in the study according to all inclusion/exclusion criteria.
- TS: All participants who received at least 1 dose of PRS-344/S095012.
- RES: All participants in the TS who had measurable disease at baseline and met any of the following conditions: 1) at least 1 postbaseline disease assessment; 2) documented clinical progression; 3) death.
- DLTES: All participants who had received at least 80% of the required Cycle 1 PRS-344/S095012 dose and completed the DLT observation period or who experienced a DLT.
- PKS: All participants who received at least 1 dose of IMP, for whom at least 1 reportable postdose PK concentration was available.
- IGS: All participants who received at least one dose of IMP and had a baseline and at least one postbaseline (preinfusion) immunogenicity assessment.

The ***efficacy analysis*** was performed on the TS and using all efficacy data before any subsequent anticancer therapy.

Study participants: Analysis of disposition of study participants was based on the ES. The size of each analysis set and reasons for exclusion is provided.

Pharmacokinetic analysis: Results will be provided in a separate PK report.

Immunogenicity analysis: Analysis of immunogenicity was performed on all participants who received at least 1 dose of PRS-344/S095012 and had baseline and at least 1 postbaseline (preinfusion) immunogenicity assessment.

Safety analysis: Full study safety analysis (i.e., AEs, laboratory data, vital signs and ECG analyses) was performed including all Phase 1 safety data and using the TS.

Summary of Results and Conclusions

Disposition of Participants:

- A total of 45 (97.8%) participants received at least 1 dose of PRS-344/S095012. One participant in the obinutuzumab + PRS-344/S095012 36 mg group did not receive PRS-344/S095012 following administration of obinutuzumab pretreatment.
- All participants were withdrawn from the study. The most frequent reasons for premature study withdrawal in all groups were progressive disease (54.3% participants overall) and AEs (30.4% participants overall). The majority of participants across groups discontinued study treatment after completing either Cycle 1 or 2.

Baseline Characteristics:

- The most frequent disease stage at primary diagnosis at baseline in the overall ES was stage IV or IVc [18 (39.1%) and 1 (2.2%) participants, respectively], followed by stage II, IIa or IIb [2 (4.3%), 5 (10.9%), and 2 (4.3%) participants, respectively] and stage III, IIIa, IIIc [5 (10.9%), 2 (4.3%), 1 (2.2%) participants, respectively].

- The primary diagnosis was colorectal cancer for 9 (19.6%) participants; other for 5 (10.9%) participants; sarcoma for 5 (10.9%) participants; cervical cancer, melanoma, non-small cell lung, cancer, pancreatic ductal adenocarcinoma, renal cell carcinoma, and urothelial cancer for 3 (6.5%) participants each; appendix cancer, breast cancer, gastro-esophageal cancer, and ovarian cancer for 2 (4.3%) participants each; and head and neck squamous cell cancer in 1 (2.2%) participant.
- For most participants, the PD-L1 status was "not available" which includes 28 (60.9%) participants with a not determined status and 7 (15.2%) participants with a missing status. Eight (17.4%) participants had negative and 3 (6.5%) participants had positive PD-L1 status.
- The overall median time from diagnosis to enrollment was 34.79 months. In the PRS-344/S095012 12 mg group, the median time was 81.81 months; in the PRS-344/S095012 60 mg group, the median time was 52.80 months; in the obinutuzumab + PRS-344/S095012 36 mg group, the median time was 35.58 months; in the PRS-344/S095012 80 mg group, the median time was 19.81 months; and in the PRS-344/S095012 36 mg group, the median time was 18.51 months.
- Most [38 (82.6%)] participants had more than 4 months disease duration from diagnosis to beginning of the study.

Extent of Exposure:

- Overall, the median duration of treatment was 0.95 months, and the median duration of exposure was 1.38 months and 2 cycles. The median cumulative dose was 120 mg.
- Twelve (26.7%) participants completed less than a month of exposure period, 16 (35.6%) participants had between 1 and 2 months of exposure, 10 (22.2%) participants had between 3 and 6 months of exposure, 4 (8.9%) participants had between 2 and 3 months of exposure, 1 (2.2%) participant had between 6 to 9 months of exposure, and 2 (4.4%) participants had more than 12 months of exposure period.
- Overall, 7 (15.6%) participants had a dose interruption, 17 (37.8%) participants had dose delays, 0 participants had dose omissions, and 9 (20.0%) participants had dose reductions.
- In PRS-344/S095012 12 mg group, there were no dose interruptions nor dose reductions. Two (50.0%) participants had once a dose delay.
- Dose reductions occurred only in PRS-344/S095012 36 mg and 60 mg groups.

Efficacy Results:

Primary Efficacy Endpoint(s)

- No primary endpoints were related to efficacy in this study.

Secondary Efficacy Endpoint(s)

- The reported secondary efficacy endpoints were ORR (RES and TS), BOR (TS), and tumor shrinkage, while DoR, PFS, and OS were not analyzed.
- One participant in the obinutuzumab + PRS-344/S095012 36 mg group had PR, and no participant in the other treatment groups had PR or CR.

Safety Results:

- A total of 8 participants (22.2%) reported DLTs during the DLT evaluation period from Cycle 1 Day 1 to Cycle 1 Day 28. At least 1 DLT was reported in all treatment groups except for PRS-344/S095012 12 mg group.
- In the PRS-344/S095012 80 mg group, 1 (33.3%) of the 3 participants experienced all the reported DLTs (haemophagocytic lymphohistiocytosis, abdominal compartment syndrome, bacterial sepsis, immune-mediated enterocolitis, multiple organ dysfunction syndrome, pulmonary haemorrhage, seizure).
- All participants in each treatment group had at least 1 treatment-emergent AE (TEAE), and all 45 participants (100%) reported TEAEs during the on-treatment period.
- Infusion related reaction was reported in 14 (31.1%) participants, and cytokine release syndrome was reported in 11 (24.4%) participants.
- A total of 40 (88.9%) participants had Grade ≥3 TEAEs in the TS.
- Overall, a total of 39 (86.7%) participants had TEAEs related to PRS-344/S095012 treatment. Infusion related reaction considered related to treatment was reported in 5 (55.6%) participants in the PRS-344/S095012 36 mg group, 4 (28.6%) participants in the PRS-344/S095012 60 mg group, 3 (50%) participants in the PRS-344/S095012 80 mg group, and 2 (16.7%) participants in the obinutuzumab + PRS-344/S095012 36 mg group.
- Cytokine release syndrome considered related to PRS-344/S095012 was reported in 3 (33.3%) participants in the PRS-344/S095012 36 mg group, 5 (35.7%) participants in the PRS-344/S095012 60 mg group, 2 (33.3%) participants in the PRS-344/S095012 80 mg group, and 1 (8.3%) participant in the obinutuzumab + PRS-344/S095012 36 mg group.
- The most frequently reported TEAEs leading to death was malignant neoplasm progression in the PRS-344/S095012 36 mg group, PRS-344/S095012 60 mg group, and PRS-344/S095012 + obinutuzumab 36 mg group.
- The TEAEs of haemophagocytic lymphohistiocytosis and pulmonary haemorrhage considered related to PRS-344/S095012 leading to death were both reported in 1 (16.7%) participant in the PRS-344/S095012 80 mg group.
- A total of 35 (77.8%) participants had at least 1 serious TEAE in the TS.
- The most frequently reported serious TEAEs were malignant neoplasm progression reported in 2 (22.2%) participants in the PRS-344/S095012 36 mg group, 5 (35.7%) participants PRS-344/S095012 60 mg group, and 4 (33.3%) participants in the PRS-344/S095012 + obinutuzumab 36 mg group; cytokine release syndrome reported in 4 (28.6%) participants in the PRS-344/S095012 60 mg group; and drug-induced liver injury reported in 3 (25.0%) participants in the obinutuzumab + PRS-344/S095012 36 mg group.
- A total of 16 (35.6%) participants had at least 1 serious TEAE related to PRS-344/S095012 in the TS. The most frequently reported serious TEAEs related to treatment were cytokine release syndrome reported in 4 (28.6%) participants in the PRS-344/S095012 60 mg group and drug-induced liver injury reported in 3 (25.0%) participants in the obinutuzumab + PRS-344/S095012 36 mg group.

- The most frequently reported TEAEs leading to treatment discontinuation were drug-induced liver injury in the obinutuzumab + PRS-344/S095012 36 mg group and cytokine release syndrome and infusion related reaction in the PRS-344/S095012 60 mg group.
- Drug-induced liver injury was reported in 3 (25%) participants and considered related to PRS-344/S095012 leading to treatment discontinuation in the obinutuzumab + PRS-344/S095012 36 mg group; 2 TEAEs were classified as a Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and 1 TEAE as Grade 4, and 2 of these were resolved and 1 was not resolved by the end of the study.
- One participant had a Grade 2 TEAE of herpes simplex reactivation in the PRS-344/S095012 60 mg group that was resolved without any changes made to treatment dose and considered not related to study treatment.
- No clinically relevant trends were observed for vital signs and clinical examination during the study. No ECG measurement was reported as a TEAE.
- There was a higher proportion of treatment-induced ADA, anti-4-1BB, and anti-PD-L1 positive results in participants across the monotherapy PRS-344/S095012 groups than in participants in the obinutuzumab + PRS-344/S095012 36 mg group. Similarly, median titer levels for treatment-induced ADA, anti-4-1BB, and anti-PD-L1 positive results were higher in participants across the monotherapy PRS-344/S095012 groups than in the obinutuzumab + PRS-344/S095012 36 mg group.

Conclusion:

This was a FIH, Phase 1/2, multicenter, open-label, dose escalation and dose expansion study designed to determine the safety and activity of PRS-344/S095012 in participants with locally advanced and/or metastatic solid tumors.

The Sponsor decided to prematurely discontinue recruitment to the CL1-95012-001 study because the overall benefit-risk balance of PRS-344/S095012 was unfavorable. The participants in Phase 1 were allowed to continue the FU until disease progression or any other reason to discontinue study treatment. The Phase 2 dose expansion of the study was not initiated.

A total of 45 participants were treated as part of the Phase 1 dose escalation across the PRS-344/S095012 12 mg (4 participants), PRS-344/S095012 36 mg (9 participants), PRS-344/S095012 60 mg (14 participants), PRS-344/S095012 80 mg (6 participants), and the obinutuzumab + PRS-344/S095012 36 mg (12 participants) groups.

In overall treated participants, the most common (reported in ≥ 20% of participants) TEAEs were fatigue, pyrexia, infusion related reaction, nausea, cytokine release syndrome, decreased appetite, malignant neoplasm progression, aspartate aminotransferase increased, alanine aminotransferase increased, and constipation. The most common (reported in ≥ 10% of participants) Grade ≥ 3 related TEAEs were lymphocyte count decreased and neutrophil count decreased. The most common (reported in ≥ 6% of participants) serious treatment-related TEAEs were cytokine release syndrome, drug-induced liver injury, and infusion related reaction.

No clear conclusion could be drawn regarding the assessed efficacy based on the analyzed secondary efficacy endpoints ORR (RES and TS), BOR (TS), and tumor shrinkage. Despite the observed clinical activity (1 PR in the obinutuzumab + PRS-344/S095012 36 mg group), the overall clinical activity of PRS-344/S095012 was modest based on the limited data.

Overall, across monotherapy PRS-344/S095012 groups, at least 75% of participants developed positive ADA titers towards anti-4-1BB and/or anti-PD-L1. In the obinutuzumab + PRS-344/S095012 36 mg group, 22% of participants (i.e., 2 out of 9 evaluable participants) developed positive ADA titers towards anti-4-1BB and /or anti-PD-L1. Of the evaluable participants, 1 participant had a single occurrence of a very low ADA titer that can be considered not significant as the following 2 ADA results were negative.

Overall, the relatively high frequency and severity of TEAEs across dose levels, the limited tolerability, high immunogenicity, and modest clinical activity supported the Sponsor's decision to discontinue recruitment into the study.

Date of the Report: 17 Dec 2025