2. SYNOPSIS

Name of Sponsors: Institut de Recherches Internationales Servier (I.R.I.S.)	*(For National Authority Use only)*
Name of Finished Product: S95033 (AG-270) **Name of Active Ingredient:** AG-270/S95033	
Title of Study: A Phase 1 Study of AG-270 in the Treatment of Subjects with Advanced Solid Tumors or Lymphoma with Homozygous Deletion of *MTAP* Protocol No.: AG270-C-001 EudraCT No.: 2017-004384-13 NCT No.: NCT03435250	
Main Investigator: Not applicable	
Number of Study Centers and Countries: Overall, 3 countries and 8 sites were involved; in the United States, 6 sites enrolled 64 participants; in Spain, 1 site enrolled 11 participants and in France, 1 site enrolled 10 participants.	
Studied Period: Initiation date: 26 February 2018 Completion date: 20 April 2023 (last participant last visit) Study enrollment was stopped on 22 June 2022; see the Study Design information for a detailed explanation of the reasons for stopping enrollment.	
Phase of Development of the Study: Phase 1	
Publication (Reference): Heist RS, Gounder MM, Postel-Vinay S, et al. A Phase 1 trial of AG-270 in patients with advanced solid tumors or lymphoma with homozygous MTAP deletion [abstract]. In: Proceedings of the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; 2019 Oct 26-30; Boston, MA. Philadelphia (PA): AACR; Mol Cancer Ther 2019;18(12 Suppl):Abstract nr PR03. doi:10.1158/1535-7163.TARG-19-PR03.	
Background and Rationale for the Study: Methylthioadenosine phosphorylase (MTAP) is a key enzyme in the methionine salvage pathway. It metabolizes a byproduct of polyamine synthesis, 5′-methylthioadenosine, which leads to the eventual regeneration of methionine and adenine. *MTAP*, the gene encoding this enzyme, is homozygously deleted in a broad range of malignancies including pancreatic ductal adenocarcinoma, non-small cell lung cancer (NSCLC), gastric cancer, esophageal cancer, bladder cancer, diffuse large B-cell lymphoma, and glioblastoma multiforme (GBM). Synthetic lethal screens in panels of cancer cell lines and in an isogenic pair of colon cancer cell lines (HCT116) have shown that cells in which *MTAP* is homozygously deleted are particularly sensitive to decreases in the concentration of the methyl donor S-adenosylmethionine (SAM). AG-270/S95033 is a small molecule inhibitor of methionine adenosyltransferase 2A (MAT2A), an enzyme that generates SAM from methionine and adenosine triphosphate. The expectation is that by treating patients with AG-270/S95033 and reducing intracellular concentrations of SAM, cancer cells with homozygous deletion of MTAP will develop a selective growth disadvantage. In enzymatic assays and cellular studies, AG-270/S95033 showed potent inhibition of MAT2A, and in most *MTAP*-deficient cancer cell lines AG-270/S95033 treatment leads to a robust decrease in cell proliferation. Cell cycle studies showed that AG-270/S95033-treated HCT116 $MTAP^{-/-}$ cells had delayed progression through the S/G2/M phases and that these cells accumulated a variety of mitotic defects, such as multinucleated and micronucleated cells, indicating a functional impairment of mitosis. In clinical practice, taxanes are widely used antimitotic agents, which act to delay or block mitotic progression by destabilization of microtubules. Both in vitro and in vivo data support the hypothesis that the combination of AG-270/S95033 with taxanes may lead to greater antitumor activity than possible with either agent given alone. This study aimed to define the optimal doses of AG-270/S95033 as a single agent in the treatment of participants with *MTAP*-deleted advanced solid tumors or lymphoma (Treatment Arm 1), in combination with docetaxel in	

the treatment of participants with *MTAP*-deleted NSCLC (Treatment Arm 2), and in combination with nab-paclitaxel and gemcitabine in the treatment of participants with *MTAP*-deleted pancreatic cancer (Treatment Arm 3).

Primary Objectives and Endpoints:

Objectives	**Endpoints**
AG-270/S95033 Monotherapy	
- To determine the maximum tolerated dose (MTD) of AG-270/S95033 and characterize its dose-limiting toxicities (DLTs) in participants with advanced solid tumors or lymphoma with homozygous deletion of *MTAP*.	- The frequency of DLTs associated with AG-270/S95033 administration during the first cycle of treatment.
AG-270/S95033 in Combination With Docetaxel	
- To determine the MTD of AG-270/S95033 in combination with docetaxel and characterize the DLTs of this combination in participants with NSCLC and other advanced solid tumors with homozygous deletion of *MTAP*.	- The frequency of DLTs associated with the combination of AG-270/S95033 and docetaxel administration during the first cycle of treatment.
AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine	
- To determine the MTD of AG-270/S95033 in combination with nab-paclitaxel and gemcitabine and characterize the DLTs of this combination in participants with advanced pancreatic cancer with homozygous deletion of *MTAP*.	- The frequency of DLTs associated with the combination of AG-270/S95033, nab-paclitaxel, and gemcitabine administration during the first cycle of treatment.

Due to the decision to stop enrollment in the study, pharmacokinetics (PK), pharmacodynamics (PD), and genomic and proteomic endpoints were not assessed. This abbreviated clinical study report presents assessments of the safety and tumor response endpoints only.

Study Design:

This was a Phase 1, multicenter, open-label study of AG-270/S95033, an oral MAT2A inhibitor, administered as a monotherapy or in combination with taxane-based chemotherapy in adult participants with advanced solid tumors or lymphoma with homozygous deletion of *MTAP*. The loss of the *MTAP* gene was inferred through genomic or fluorescence in situ hybridization (FISH) data indicating homozygous loss of cyclin-dependent kinase inhibitor 2A (*CDKN2A)*, given the high concordance between the loss of *CDKN2A* and *MTAP*, or by immunohistochemical evaluation of tumor tissue indicating loss of expression of the *MTAP* protein.

This study had 3 treatment arms, one evaluating AG-270/S95033 given as a single agent and 2 others evaluating AG-270/S95033 given in combination with standard taxane-based chemotherapy. Each treatment arm was to include a dose escalation phase followed by a dose expansion phase; however, due to the decision to stop enrollment, only the dose escalation phase was performed in each treatment arm.

AG-270/S95033 Monotherapy (Treatment Arm 1)

- This treatment arm of the study included a dose escalation phase for the evaluation of AG-270/S95033 as a single agent. The dose escalation phase was designed to determine the MTD of AG-270/S95033. However, if an MTD could not be determined, then the aim was to determine the dose with maximum pharmacologic activity (eg, maximum suppression of circulating concentrations of SAM) or a maximum feasible dose. A 2-parameter adaptive Bayesian Logistic Regression Model (BLRM) using escalation with overdose control (EWOC) was used to guide dose escalation and to estimate the MTD of AG-270/S95033.
- This treatment arm enrolled participants with advanced solid tumors or lymphoma with homozygous deletion of *MTAP*. Participants eligible for this arm of the study were required to have disease that had progressed in spite of prior treatments and for which additional effective (curative or life-prolonging) standard treatment was not available. Participants whose disease was stable or improved were allowed to continue treatment with AG-270/S95033, assuming that they were tolerating it well. In general, participants who experienced documented disease progression or unacceptable treatment-related toxicity had therapy with AG-270/S95033 discontinued.

AG-270/S95033 in Combination With Docetaxel (Treatment Arm 2)

- Following the identification of a pharmacologically active and safe single-agent dose of AG-270/S95033, the combination of AG-270/S95033 with docetaxel was evaluated, primarily in participants with *CDKN2A*- and/or *MTAP*-deleted NSCLC that has progressed after no more than 2 previous lines of cytotoxic chemotherapy for metastatic (Stage 4) disease.
- AG-270/S95033 was given on a daily basis as a single agent for 1 week to achieve close to steady-state systemic exposure and reductions in plasma SAM concentrations before the first dose of docetaxel was administered. Upon completion of this first week of AG-270/S95033 treatment, the first dose of docetaxel was administered while daily administration of AG-270/S95033 continued. The PK of both docetaxel and AG-270/S95033 was evaluated in this combination.
- A separate 5-parameter adaptive BLRM using the EWOC principle was used to guide dose escalation and to estimate the MTD of the combination of AG-270/S95033 and docetaxel.

AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine (Treatment Arm 3)

- Following the identification of a pharmacologically active and safe single-agent dose of AG-270/S95033, the combination of AG-270/S95033 with nab-paclitaxel and gemcitabine was evaluated in participants with *CDKN2A*- and/or *MTAP*-deleted locally advanced or metastatic pancreatic ductal adenocarcinoma who had not been previously treated with more than 1 line of cytotoxic chemotherapy for advanced or metastatic disease.
- AG-270/S95033 was given on a daily basis as a single agent for 1 week to achieve close to steady-state systemic exposure and reductions in plasma SAM concentrations before the first doses of nab-paclitaxel and gemcitabine were administered. Upon completion of this first week of AG-270/S95033 treatment, the first doses of nab-paclitaxel and gemcitabine were administered while daily administration of AG-270/S95033 continued. The PK of both nab-paclitaxel and AG-270/S95033 was evaluated in this combination.
- A separate 5-parameter adaptive BLRM using the EWOC principle was used to guide dose escalation and to estimate the MTD of the combination of AG-270/S95033 and docetaxel.

Study enrollment was terminated during evaluation of dose escalation in Treatment Arm 3 (AG-270/S95033 in combination with nab-paclitaxel and gemcitabine) because the Sponsor decided to discontinue the AG-270/S95033 clinical development program. This decision was not taken because of concerns regarding the safety of the study drug AG-270/S95033. At the time that this decision was issued (22 June 2022), the MTD of AG-270/S95033 as a single agent and in combination with docetaxel had been reached in Treatment Arms 1 and 2 of the study, respectively. The Sponsor decided to stop enrollment into the study based on strategy change. All treatments and assessments continued to be provided, per the protocol, for the participant remaining on-treatment at the time of the decision.

This study was performed in strict accordance with Good Clinical Practice (GCP).

Number of Participants (Planned and Analyzed):

Planned:

In total, approximately 138 participants were planned to be enrolled in the study:

- AG-270/S95033 monotherapy: approximately 54 participants with advanced solid tumors or lymphoma with homozygous deletion of MTAP (42 in the dose escalation phase; 12 in the dose expansion phase)
- AG-270/S95033 in combination with docetaxel: approximately 40 participants with NSCLC and other advanced solid tumors with homozygous deletion of MTAP (a minimum of 15 in the dose escalation phase; up to 25 in the dose expansion phase)
- AG-270/S95033 in combination with nab-paclitaxel and gemcitabine: approximately 44 participants with advanced pancreatic cancer with homozygous deletion of MTAP (a minimum of 15 in the dose escalation phase; up to 29 in the dose expansion phase)

Analyzed:

In total, 83 participants were enrolled and received treatment with AG-270/S95033 as monotherapy or in combination with taxane-based chemotherapy:

- AG-270/S95033 monotherapy: a total of 40 participants were included in the study
  - Safety Analysis Set (SAS): 40 participants
  - Full Analysis Set (FAS): 40 participants
  - Dose Determining Set 1 (DDS1): 33 participants
- AG-270/S95033 in combination with docetaxel: a total of 25 participants were included in the study
  - SAS: 25 participants
  - FAS: 25 participants

○ Dose Determining Set 2 (DDS2): 22 participants - AG-270/S95033 in combination with nab-paclitaxel and gemcitabine: a total of 18 participants were included in the study ○ SAS: 18 participants ○ FAS: 18 participants ○ Dose Determining Set 3 (DDS3): 15 participants
Diagnosis and Main Criteria for Inclusion: - AG-270/S95033 Monotherapy: Have histologically confirmed diagnosis of an advanced solid tumor or lymphoma that had progressed in spite of at least one prior line of treatment, and for which additional effective standard therapy was not available. For this study, effective standard therapy was defined as treatment that has been shown to be curative and/or to prolong survival. In addition, participants who were considered to not be candidates for standard therapy or who declined standard therapy were eligible for this study; in such cases, documentation of the reason for omitting or declining a standard therapy was required. - AG-270/S95033 in Combination With Docetaxel: Have histologically confirmed diagnosis of NSCLC that had been previously treated with cytotoxic chemotherapy, but with no more than 2 prior lines of cytotoxic chemotherapy in the setting of metastatic (Stage 4) disease. Three prior lines of cytotoxic chemotherapy for metastatic disease were allowed if one of the 3 lines was a maintenance treatment. Participants with solid tumors other than NSCLC for which docetaxel was indicated were eligible for the dose escalation arm, but they also must have received no more than 2 prior lines of cytotoxic chemotherapy in the setting of metastatic disease. For both participants with NSCLC and participants with other malignancies prior treatment with taxanes was permitted, but prior treatment with docetaxel was not allowed. There was no limitation on the number of non-cytotoxic therapies that a participant with NSCLC or with another malignancy may have received. - AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: Have locally advanced or metastatic pancreatic ductal adenocarcinoma. Have received no more than 1 previous line of cytotoxic chemotherapy for advanced or metastatic disease if enrolled into the dose escalation phase of the study and have received no prior cytotoxic chemotherapy for advanced or metastatic disease if enrolled into the dose expansion phase of the study. There was no limitation on the number of non-cytotoxic therapies that a subject may have received. Treatment with cytotoxic chemotherapy in the adjuvant setting were not counted in the lines of previous cytotoxic chemotherapy for advanced or metastatic disease. However, for a participant to be eligible for the dose expansion phase of this study the final dose of adjuvant cytotoxic chemotherapy must have been given at least 6 months before administration of the first doses of AG-270, nab-paclitaxel, and gemcitabine. No minimum period of time between the final dose of adjuvant cytotoxic chemotherapy and the first doses of the study drugs is required for a participant to be enrolled in the dose escalation phase of this arm. - All Treatment Arms (AG-270/S95033 Monotherapy, AG-270/S95033 in Combination With Docetaxel, and AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine): Have evidence of homozygous loss of *CDKN2A* and/or *MTAP* in the participant's tumor tissue. i. Local results from DNA sequencing or FISH analysis indicating homozygous loss of *CDKN2A* and/or *MTAP* were acceptable for a participant's enrollment. ii. If the status of *CDKN2A* and *MTAP* was unknown, archival or fresh tumor tissue must have been evaluated by the central laboratory and shown to have loss of *MTAP* by immunohistochemistry (IHC). iii. There was no limit on the time between the acquisition of the tumor tissue showing the loss of *CDKN2A* and/or *MTAP* and the assessment of a participant's eligibility for this study: the loss of *CDKN2A*/*MTAP* is an early, truncal event in tumorigenesis. iv. Participants enrolled in the dose expansion arm must have had evidence of homozygous deletion of *MTAP* from their tumor cells as determined by central IHC evaluation.

Study Drug:
AG-270/S95033 was supplied as 25 and 100 mg strength tablets to be taken orally on an empty stomach. The optimal dosage within each treatment arm was to be determined during this study. The intended frequency of AG-270/S95033 dosing was once daily, with provision for twice daily dosing should the PK, PD, or safety profile of AG-270/S95033 suggest that twice daily dosing could be advantageous.

- AG-270/S95033 Monotherapy: A single dose of AG-270/S95033 was administered on Cycle 0, Day -3 (C0D-3) with no further dosing over the subsequent 72 hours. This initial single dose of AG-270/S95033 facilitated characterization of the elimination half-life of AG-270/S95033. Daily dosing with AG-270/S95033 then began on C1D1. For the purpose of scheduling study assessments and making decisions about dose escalation, 1 cycle of therapy was defined as 28 days of daily treatment with AG-270/S95033.
- AG-270/S95033 in Combination With Docetaxel: Docetaxel was given using the standard approved dose of 75 mg/m^2 intravenous (IV) every 3 weeks, with provision made for a reduction in its dose to 55 mg/m^2 should a DLT related to docetaxel have occurred. An initial docetaxel dose of 55 mg/m^2 may have also been evaluated, with provision made for reduction in its dose to 40 mg/m^2 should a DLT related to docetaxel have occurred. Daily dosing with AG-270/S95033 alone occurred for 1 week before the first dose of docetaxel was administered. The first dose of AG-270/S95033 was given in the clinic on Cycle 0, Day -7 (C0D-7), and the first dose of docetaxel was administered on C1D1. Cycles of combined therapy with AG-270/S95033 and docetaxel had a planned duration of 21 days.
- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: The doses of nab-paclitaxel and gemcitabine given in combination with AG-270/S95033 conformed to those that are approved for the treatment of metastatic pancreatic cancer: nab-paclitaxel at 125 mg/m^2 IV and gemcitabine at 1000 mg/m^2 IV. Provision was also made for evaluating lower initial doses of nab-paclitaxel and gemcitabine (ie, 100 mg/m^2 and 800 mg/m^2, respectively). Cycles of combined therapy with AG-270/S95033 and nab-paclitaxel and gemcitabine had a planned duration of 28 days, with nab-paclitaxel and gemcitabine administered on Days 1, 8, and 15 of each 28-day cycle (gemcitabine to be administered after nab-paclitaxel). Daily dosing with AG-270/S95033 alone occurred for 1 week before the first doses of nab-paclitaxel and gemcitabine were administered. The first dose of AG-270/S95033 was given in the clinic on C0D-7, and the first doses of nab-paclitaxel and gemcitabine were administered on C1D1.

Comparator:
Not applicable

Duration of Treatment:
Cycles of treatment with AG-270/S95033 (either as monotherapy or in combination with standard taxane-based chemotherapy) were repeated as long as the participant's disease was stable or improved and the participant was tolerating the treatment well.

Statistical Methodology:

Study participants:

Disposition, demographic, and baseline disease characteristic data were summarized descriptively by dose level/schedule within the relevant treatment arm and listed by participant using the FAS (all participants who were enrolled and received at least 1 dose of study treatment [AG-270/S95033 as monotherapy; AG-270/S95033 in combination with docetaxel; or AG-270/S95033 in combination with nab-paclitaxel and gemcitabine]).

Treatments:

Study drug exposure, including number of doses administered, total dose, duration of treatment, and the proportion of participants with dose modifications were listed and summarized using descriptive statistics by dose level/schedule within the relevant treatment arm. Concomitant medications and significant non-drug therapies prior to and after the start of the study drug were listed by participant and summarized by the Anatomical Therapeutic Chemical Classification term and by dose level/schedule within the relevant treatment arm by means of contingency tables. The primary analysis set was the SAS (all participants who were enrolled and received at least 1 dose of study treatment [AG-270/S95033 as monotherapy; AG-270/S95033 in combination with docetaxel; or AG-270/S95033 in combination with nab-paclitaxel and gemcitabine]).

Safety analyses:

- For estimation of the MTD, the analysis method was an adaptive BLRM guided by the EWOC principle. Estimation of the MTD will be based upon the estimation of the probability of DLT in Cycle 1 for participants in the DDS1 (AG-270/S95033 monotherapy), DDS2 (AG-270/S95033 in combination with docetaxel), or DDS3 (AG-270/S95033 in combination with nab-paclitaxel and gemcitabine).
    - DLTs were listed and their incidence summarized by Medical Dictionary for Regulatory Activities (MedDRA) primary System Organ Class (SOC) and/or Preferred Term (PT), worst

grade based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, type of adverse event (AE), and dose level/schedule.

- The SAS was used for all listings and summaries of safety data.
  - Adverse events: treatment-emergent adverse events (TEAEs) are AEs with a first onset date during the on-treatment period or worsening from baseline. Unless otherwise specified, TEAEs were summarized according to the latest version of MedDRA by SOC and/or PT, severity (based on CTCAE Version 4.03 grading), seriousness, and relation to study treatment in decreasing frequency based on the frequencies observed for all participants in each treatment arm.
  - Deaths: the frequency of participants in the SAS who died, along with the cause of death, was tabulated based on information from the Death Report eCRF.
  - Clinical laboratory data: for all laboratory tests (chemistry, hematology, coagulation), the actual values and the changes from baseline were summarized by study visit and time point. For laboratory tests covered by the CTCAE Version 4.03, laboratory data were graded accordingly. For laboratory tests where grades are not defined by CTCAE, results were graded by the low/normal/high classifications based on laboratory normal ranges.
  - Physical measurements and vital sign assessments (height, weight, systolic blood pressure, diastolic blood pressure, heart rate, pulse oximetry, respiratory rate, temperature): the actual values and relevant changes from baseline were summarized by study visit.
  - Electrocardiograms (ECG): summaries included all ECG assessments from the on-treatment period. The following analyses will be performed for each applicable ECG parameter (RR, PR, QRS, QT, and QTc) during the on-treatment period.
  - Performance scores: the Eastern Cooperative Oncology Group (ECOG) performance status shift from baseline to highest score during the on-treatment period was summarized.
  - Ophthalmic examination: a by participant listing was presented for each ophthalmologic examination (best corrected visual acuity, pupillary light reflexes, intraocular pressure, dilated fundoscopic examination with fundus photography, ocular coherence tomography, and retinal autofluorescence).

Efficacy Analyses:

The following analyses were based on the FAS, unless otherwise specified. Clinical activity was assessed based on best overall response (BOR), objective response (OR), and duration of response (DoR). Response to treatment was assessed by the investigators using RECIST Version 1.1 for solid tumors and 2014 Lugano criteria for lymphomas.

Summary of Results and Conclusions

Disposition of participants:

Overall, a total of 83 participants were enrolled and received any treatment with the following therapies: 40 participants with AG-270/S95033 monotherapy, 25 with AG-270/S95033 in combination with docetaxel, and 18 with AG-270/S95033 in combination with nab-paclitaxel and gemcitabine. The overall disposition of enrolled participants by treatment arm is presented in Table 1.

Table 1 - Overall participant disposition by treatment arm – Full Analysis Set

	AG-270/S95033 monotherapy n (%)	AG-270/S95033 in combination with docetaxel n (%)	AG-270/S95033 in combination with nab-paclitaxel and gemcitabine n (%)
Treatment status			
On-treatment	0	0	0
Discontinued treatment	40 (100)	25 (100)	18 (100)
Primary reason for treatment discontinuation			
Adverse event	2 (5.0)	2 (8.0)	2 (11.0)
Physician decision	-	1 (4.0)	-
Death	1 (2.5)	-	1 (5.6)
Progressive disease	28 (70.0)	19 (76.0)	11 (61.1)
Withdrawal by participant	4 (10.0)	-	-
Clinical suspicion of disease progression	5 (12.5)	2 (8.0)	4 (22.2)

Other: patient was barely arousable and was admitted to emergency room and later on passed away	-	1 (4.0)	-
Discontinued treatment (AG-270/S95033)	-	25 (100)	18 (100)
Primary reason for treatment (AG-270/S95033) discontinuation			
Adverse event	-	4 (16.0)	3 (16.7)
Death	-	-	1 (5.6)
Physician decision	-	1 (4.0)	-
Progressive disease	-	16 (64.0)	10 (55.6)
Clinical suspicion of disease progression	-	3 (12.0)	4 (22.2)
Other: patient was barely arousable and was admitted to emergency room and later on passed away	-	1 (4.0)	-
Discontinued treatment (Docetaxel)	-	24 (96.0)	-
Primary reason for treatment (Docetaxel) discontinuation			
Adverse event	-	5 (20.0)	-
Physician decision	-	1 (4.0)	-
Progressive disease	-	16 (64.0)	-
Clinical suspicion of disease progression	-	2 (8.0)	-
Discontinued treatment (nab-Paclitaxel)	-	-	16 (88.9)
Primary reason for treatment (nab-Paclitaxel) discontinuation			
Adverse event	-	-	2 (11.1)
Death	-	-	1 (5.6)
Progressive disease	-	-	10 (55.6)
Clinical suspicion of disease progression	-	-	3 (16.7)
Discontinued treatment (Gemcitabine)	-	-	16 (88.9)
Primary reason for treatment (Gemcitabine) discontinuation			
Adverse event	-	-	1 (5.6)
Death	-	-	1 (5.6)
Progressive disease	-	-	11 (61.1)
Clinical suspicion of disease progression	-	-	3 (16.7)
Study status			
On study	0	0	0
Discontinued study	40 (100)	25 (100)	18 (100)
Primary reason for study discontinuation			
Adverse event	1 (2.5)	-	1 (5.6)
Death	12 (30.0)	5 (20.0)	3 (16.7)
Physician decision	-	1 (4.0)	-
Lost to follow-up	2 (5.0)	-	-
Progressive disease	17 (42.5)	15 (60.0)	6 (33.3)
Withdrawal by participant	7 (17.5)	2 (8.0)	3 (16.7)
Other: participant switched to arm	1 (2.5)	-	-
Clinical suspicion of disease progression	-	2 (8.0)	2 (11.1)
Other: completed follow-up assessment	-	-	1 (5.6)
Other: completed follow-up	-	-	1 (5.6)
Other: protocol-defined follow-up is completed	-	-	1 (5.6)

Full Analysis Set all participants who were enrolled and received at least 1 dose of study treatment, classified according to the dose level and schedule assigned.
Treatment status defined as whether participants have discontinued study treatment with AG-270/S95033 in combination with Docetaxel as combotherapy or only AG-270/S95033 or docetaxel; in combination with nab-paclitaxel and gemcitabine as combotherapy or only AG-270/S95033 or nab-paclitaxel or gemcitabine.
Study status defined as whether participants have discontinued treatment with AG-270/S95033 and have been followed 28 days after the last dose for safety assessments or have died, been lost to follow-up, or withdrawn consent.
Percentages were based on the number of participants in the Full Analysis Set in each column (denominator).

Baseline characteristics:

- AG-270/S95033 Monotherapy: The most frequent primary tumor diagnosis were bile duct cancer and pancreatic cancer (experienced by 17.5% of the participants, each). The most frequent primary tumor stage at initial diagnosis and at screening was IV in 19 participants (47.5%) and 36 participants (90.0%), respectively. ECOG performance status at screening was 1 in the majority of the participants (26 participants, 65.0%), and regarding MTAP IHC test result at screening it was less than or equal to 20% positive in 23 participants (57.5%). The most frequent CDKN2A test result at screening was homozygously deleted experienced by 35 participants (87.5%) and among these the most frequent MTAP status was less than or equal to 20% positive in 18 participants (51.4%).
- AG-270/S95033 in Combination With Docetaxel: The most frequent primary tumor diagnosis were esophagus cancer and non-small cell lung cancer cancer (experienced by 16.0% of the participants, each). The most frequent primary tumor stage at initial diagnosis was III in 9 participants (36.0%) and at screening was IV in 20 participants (80.0%). ECOG performance status at screening was 1 in the majority of the participants (18 participants, 72.0%), and regarding MTAP IHC test result at screening it was greater than 20% positive in 12 participants (48.0%). The most frequent CDKN2A test result at screening was homozygously deleted experienced by 24 participants (96.0%) and among these the most frequent MTAP status was greater than 20% positive in 12 participants (50.0%).
- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: The primary tumor diagnosis was pancreatic cancer for all 18 participants (100.0%). The most frequent primary tumor stage at initial diagnosis and at screening was IV in 12 participants (66.7%) and 16 participants (88.9%), respectively. ECOG performance status at screening was 0 in the majority of the participants (11 participants, 61.1%), and regarding MTAP IHC test result at screening it was less than or equal to 20% positive in 10 participants (55.6%). The most frequent CDKN2A test result at screening was homozygously deleted experienced by 16 participants (88.9%) and among these the most frequent status was less than or equal to 20% positive in 8 participants (50.0%).
- All Treatment Arms: Disease characteristics of participants at baseline in the FAS with AG-270/S95033 monotherapy or in combination with taxane-based chemotherapy were generally similar across the different dose levels.

Extent of exposure:

- AG-270/S95033 Monotherapy: Overall, the mean (standard deviation [SD]) duration of treatment exposure with AG-270/S95033 monotherapy was 3.1 (5.76) months with a cumulative dose of 15123.8 (21573.39) mg. The mean actual dose intensity was 5916.2 (3521.58) mg/month. Overall, 25 participants (62.5%) had at least one dose interruption with AG-270/S95033 monotherapy and most of them had a reason as 'per protocol'. Four participants (10.0%) had at least one dose reduction with AG-270/S95033 monotherapy and most of them had a reason as 'per protocol'.
- AG-270/S95033 in Combination With Docetaxel: Overall, the mean (SD) duration of treatment exposure with AG-270/S95033 was 3.4 (2.91) months with a cumulative dose of 12366.0 (9446.39) mg. The mean actual dose intensity was 3965.3 (1072.84) mg/month. The mean (SD) duration of treatment exposure with docetaxel was 3.1 (2.53) months with a cumulative dose of 510.8 (438.76) mg. The mean actual dose intensity was 161.4 (433.77) mg/month. Overall, 18 participants (72.0%) had at least one dose interruption with AG-270/S95033 and most of them had a reason as 'per protocol'. Two participants (8.0%) had at least one dose reduction with AG-270/S95033 and both of them had a reason as 'per protocol'. Four participants (16.0%) had at least one dose interruption with docetaxel and all of them had a reason as 'per protocol'. Thirteen participants (52.0%) had at least one dose reduction with docetaxel and most of them had a reason as 'per protocol'.
- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: Overall, the mean (SD) duration of treatment exposure with AG-270/S95033 was 4.3 (5.36) months with a cumulative dose of 14741.7 (14088.50) mg. The mean actual dose intensity was 4016.8 (1322.54) mg/month. The mean (SD) duration with nab-paclitaxel was 4.4 (5.36) months with a cumulative dose of 1665.7 (1514.72) mg. The mean actual dose intensity was 448.2 (161.10) mg/month. The mean (SD) duration of treatment exposure with gemcitabine was 4.5 (5.45) months with a cumulative dose of 13571.6 (12372.90) mg. The mean actual dose intensity was 3570.5 (1296.77) mg/month. Overall, 14 participants (77.8%) had at least one dose interruption with AG-270/S95033 and most of them had a reason as 'per protocol'. Eight participants (44.4%) had at least one dose reduction with AG-270/S95033 and most of them had a reason as 'per protocol'. Fourteen participants (77.8%) had at least one dose interruption with nab-paclitaxel and most of them had a reason as 'per protocol'. Twelve participants (66.7%) had at least one dose reduction with nab-paclitaxel and most of them had a reason as 'per protocol'. Fourteen participants (77.8%) had at least one dose interruption with gemcitabine and most of them had a reason

as 'per protocol'. Twelve participants (66.7%) had at least one dose reduction with gemcitabine and most of them had a reason as 'per protocol'.

Efficacy results:

In summary, few participants had an OR in any of the treatment groups. Two participants treated with AG-270/S95033 monotherapy and 1 participant treated with AG-270/S95033 in combination with nab-paclitaxel and gemcitabine had a PR. No participant had a complete response (CR). The most common BOR was stable disease in participants treated with AG-270/S95033 in combination with taxane-based chemotherapy, and progressive disease in participants treated with AG-270/S95033 monotherapy. There was no evident relationship between tumor response and AG-270/S95033 dose level.

Antitumor activity of AG-270/S95033 monotherapy included 1 PR in a participant with sex cord stromal cell cancer (lasting 3 years) and 1 PR in a participant with non-small cell lung cancer (lasting 48 weeks). For AG-270/S95033 in combination with docetaxel, antitumor activity included 1 PR in a participant with esophageal cancer (lasting 16 weeks); however, the BOR was not evaluable for this participant. For AG-270/S95033 in combination with nab-paclitaxel and gemcitabine, antitumor activity included 1 PR in a participant with pancreatic cancer (lasting 96 weeks).

Safety results:

Dose-limiting toxicities (DLTs)

- AG-270/S95033 Monotherapy: The following 4 participants experienced at least 1 DLT during Cycle 1:
  - Serious Grade 2 hypersensitivity in 1 participant receiving 100 mg once a day (QD)
  - Serious Grade 3 hyperbilirubinaemia and serious Grade 3 rash maculo-papular in 1 participant receiving 150 mg QD
  - Non-serious Grade 3 neutrophil count decreased in 1 participant receiving 200 mg QD
  - Serious Grade 3 drug-induced liver injury and non-serious Grade 3 rash in 1 participant receiving 200 mg two times a day (BID), suggestive of an immune-allergic hepatitis (associated with eosinophilia and eosinophils at liver biopsy).

  All of the DLT AEs were considered resolved except for the Grade 3 hyperbilirubinaemia. The MTD for AG-270/S95033 monotherapy was determined to be 200 mg QD.
- AG-270/S95033 in Combination With Docetaxel: The following 6 participants experienced at least 1 DLT during Cycle 1:
  - 3 participants receiving AG-270/S95033 150 mg QD + docetaxel 75 mg/m^2
    - Serious Grade 4 febrile neutropenia in 1 participant
    - Serious Grade 3 vomiting in 1 participant
    - Serious Grade 3 diarrhoea and non-serious Grade 1 retinal degeneration in 1 participant
  - 1 participant receiving AG-270/S95033 150 mg QD + docetaxel 55 mg/m^2
    - Non-serious Grade 4 thrombocytopenia in 1 participant
  - 2 participants receiving AG-270/S95033 200 mg QD + docetaxel 75 mg/m^2
    - Non-serious Grade 4 febrile neutropenia in 1 participant
    - Non-serious Grade 3 stomatitis in 1 participant

  All of the DLT AEs were considered resolved except for the Grade 1 retinal degeneration. The MTD for AG-270/S95033 in combination with docetaxel was determined to be 150 mg QD.
- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: The following 5 participants experienced at least 1 DLT during Cycle 1:
  - 3 participants receiving AG-270/S95033 150 mg QD + nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2
    - Serious Grade 4 septic shock, non-serious Grade 4 neutrophil count decreased, and non-serious Grade 4 thrombocytopenia in 1 participant
    - Non-serious Grade 4 platelet count decreased in 1 participant
    - Non-serious Grade 4 platelet count decreased, non-serious Grade 3 platelet count decreased, and non-serious Grade 4 neutrophil count decreased in 1 participant
  - 2 participants receiving AG-270/S95033 200 mg QD + nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2
    - Non-serious Grade 3 alanine aminotransferase (ALT) increased and non-serious Grade 3 aspartate aminotransferase (AST) increased in 1 participant
    - Serious Grade 4 thrombocytopenia in 1 participant

  All of the DLT AEs were considered resolved. The MTD for AG-270/S95033 in combination with nab-paclitaxel and gemcitabine had not been determined at the time study enrollment was stopped.

Treatment-emergent adverse events (TEAEs)

Main results for AEs in the SAS are described in Table 2.

Table 2 – Overall summary of treatment-emergent adverse events by treatment arm – Safety Analysis Set

	AG-270/S95033 monotherapy n (%)	AG-270/S95033 in combination with docetaxel n (%)	AG-270/S95033 in combination with nab-paclitaxel and gemcitabine n (%)
Participants with Any TEAE	40 (100.0)	25 (100.0)	18 (100.0)
Participants with Any Treatment-Related TEAE	28 (70.0)	24 (96.0)	17 (94.4)
Serious TEAE	23 (57.5)	17 (68.0)	7 (38.9)
Serious Treatment-Related TEAE	4 (10.0)	10 (40.0)	2 (11.1)
Participants with Any TEAE Leading to Permanent Treatment Discontinuation	3 (7.5)	9 (36.0)	7 (38.9)
AE Leading to Death	1 (2.5)	1 (4.0)	0
On-treatment	1 (2.5)	1 (4.0)	0
Post-treatment	0	0	0

Safety Analysis Set all participants who were enrolled and received at least 1 dose of study treatment, classified according to the dose level and schedule received.
TEAE Treatment-emergent AE is defined as any adverse event that begins or worsens on or after the start of study drug through 28 days after the last dose of study drug.
On-treatment death is defined as any death that occurs within 28 days of last dose of study treatment.
Post-treatment death is defined as any death that occurs more than 28 days after the last dose of study treatment.
Percentages are based on the number of participants in the Safety Analysis Set in each column (denominator).

- AG-270/S95033 Monotherapy: All of the 40 participants treated with AG-270/S95033 monotherapy experienced at least 1 TEAE. The ***most frequently reported TEAEs*** (experienced by at least 25% of participants) included fatigue (17 [42.5%] participants) and nausea (13 [32.5%] participants). Overall, 28 of 40 participants (70.0%) experienced ***treatment-related TEAEs***, of whom most (21 [52.5%] participants) experienced treatment-related TEAEs of Grade 1-2 in severity. The most common (in ≥ 25% of participants) treatment-related TEAE was fatigue (10 [25.0%] participants). There were no meaningful differences in incidence of treatment-related TEAEs between the dose level groups. Twelve participants (30.0%) in the AG-270/S95033 treatment arm ***died*** during the study. Eleven of these participants (27.5%) died due to disease progression. One participant (2.5%) who received 200 mg QD died due to a fatal AE of pneumonia (verbatim term: nosocomial pneumony) which was considered not related to AG-270/S95033; this death was considered on-treatment since it occurred within 28 days of the last dose of study treatment. Another participant who received 200 mg QD experienced a fatal AE of sepsis (verbatim term: sepsis related to disease progression); the underlying cause of the sepsis was considered to be disease progression, so the cause of death for this participant was not recorded as an AE. Serious AEs (SAEs) were experienced by 23 of the 40 participants (57.5%). The ***most common SAEs*** (in >1 participant) were dyspnoea and pneumonia (3 [7.5%] participants each), and abdominal pain, liver injury, pancreatitis, sepsis, and tumour pain (2 [5.0%] participants each). Two participants (5.0%) experienced ***fatal SAEs***. Four participants (10.0%) experienced ***treatment-related SAEs***. Three participants (7.5%) ***experienced TEAEs leading to permanent treatment discontinuation.*** TEAEs leading to discontinuation were experienced by participants who received 200 mg AG-270/S95033 and included nausea, vomiting and sepsis, each in 1 participant who received 200 mg QD, and liver injury in 1 participant who received 200 mg BID, suggestive of an immune-allergic hepatitis.
- AG-270/S95033 in Combination With Docetaxel: All of the 25 participants treated with AG-270/S95033 in combination with docetaxel experienced at least 1 TEAE. The ***most frequently reported TEAEs*** (experienced by at least 25% of participants) included anaemia and diarrhoea (13 [52.0%] participants each), neutrophil count decreased (11 [44.0%] participants), alopecia (8 [32.0%] participants), and decreased appetite, fatigue, and stomatitis (7 [28.0%] participants each). Almost all of the participants (24 of 25 participants [96.0%]) experienced ***treatment-related TEAEs***, of whom most (20 [80.0%] participants) experienced treatment-related TEAEs of Grade ≥ 3 in severity. The most common (in ≥ 25% of participants) treatment-related TEAEs were anaemia and neutrophil count decreased (11 [44.0%]

participants each), diarrhoea (10 [40.0%] participants), and alopecia and fatigue (7 [28.0%] participants each). There were no meaningful differences in incidence of treatment-related TEAEs between the dose level groups. Five participants (20.0%) in the AG-270/S95033 in combination with docetaxel treatment arm ***died*** during the study. Three of these participants (12.0%) died due to disease progression. One participant (4.0%) who received AG-270/S95033 150 mg QD + docetaxel 75 mg/m^2 died due to a fatal AE of cardio-respiratory arrest which was considered not related to AG-270/S95033; this death was considered on-treatment since it occurred within 28 days of the last dose of study treatment. One participant (4.0%) who received AG-270/S95033 150 mg QD died on-treatment due to 'other' reasons; the cause of death was unknown, but it was not due to the underlying malignancy. SAEs were experienced by 17 of the 25 participants (68.0%). The ***most common SAEs*** (in >1 participant) were diarrhoea, dyspnoea, hypoxia, pneumonia, and thrombocytopenia (2 [8.0%] participants each). One participant (4.0%) experienced ***fatal SAEs***. Ten participants (40.0%) experienced ***treatment-related SAEs***. Nine participants (36.0%) experienced ***TEAEs leading to permanent discontinuation*** of study treatment (AG-270/S95033 and/or docetaxel). There were no notable differences in the incidence of TEAEs leading to treatment discontinuation between the dose levels.

- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: All of the 18 participants treated with AG-270/S95033 in combination with nab-paclitaxel and gemcitabine experienced at least 1 TEAE. The ***most frequently reported TEAEs*** (experienced by at least 25% of participants) included anaemia (10 [55.6%] participants), ALT increased, alopecia, diarrhoea, neutrophil count decreased, platelet count decreased, and vomiting (7 [38.9%] participants each), AST increased, constipation, nausea, neutropenia, thrombocytopenia (6 [33.3%] participants each), and fatigue and peripheral sensory neuropathy (5 [27.8%] participants each). Almost all of the participants (17 of 18 participants [94.4%]) experienced ***treatment-related TEAEs***, of whom most (13 [72.2%] participants) experienced treatment-related TEAEs of Grade ≥ 3 in severity. The most common (in ≥ 25% of participants) treatment-related TEAEs were alopecia, anaemia, neutrophil count decreased, platelet count decreased, and vomiting (7 [38.9%] participants each), ALT increased, diarrhoea, neutropenia, and thrombocytopenia (6 [33.3%] participants each), and fatigue, nausea, and peripheral sensory neuropathy (5 [27.8%] participants each). There were no meaningful differences in incidence of treatment-related TEAEs between the dose level groups. Three participants (16.7%) in the AG-270/S95033 in combination with nab-paclitaxel and gemcitabine arm ***died*** during the study. Two of these participants (11.1%) died due to disease progression. One participant (5.6%) who received AG-270 200 mg QD + nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 experienced a fatal AE of sudden death where the cause of death was reported as 'other' reasons and was not due to the underlying malignancy or considered related to study treatment. SAEs were experienced by 7 of the 18 participants (38.9%). The ***most common SAEs*** (in >1 participant) were pyrexia and septic shock (2 [11.1%] participants each). One participant (5.6%) experienced a ***fatal SAE***. Two participants (11.1%) experienced ***treatment-related SAEs***. Seven participants (38.9%) experienced ***TEAEs leading to permanent discontinuation*** of study treatment (AG-270/S95033, nab-paclitaxel, and/or gemcitabine). There were no notable differences in the incidence of TEAEs leading to treatment discontinuation between the dose levels.

Laboratory tests

Hematology

- AG-270/S95033 Monotherapy: For the majority of parameters assessed, there were a low number of shifts from baseline in toxicity grades. Parameters with a higher incidence of shifts to worse toxicity grades included hemoglobin (low), lymphocytes (low), and platelets (low). There were no meaningful differences in the incidence of shifts to higher toxicity grades for hematology parameters between the dose level groups. The ***most common TEAEs associated with hematology parameters*** (in > 10% of participants) were anaemia (8 [20.0%] participants), and platelet count decreased and thrombocytopenia (4 [10.0%] participants each).
- AG-270/S95033 in Combination With Docetaxel: For the majority of parameters assessed, shifts from baseline in toxicity grades indicating worsening were reported for most participants. Parameters with a higher incidence of shifts to worse toxicity grades included hemoglobin (low), leukocytes (low), lymphocytes (low) neutrophils (low), and platelets (low). There were no meaningful differences in the incidence of shifts to higher toxicity grades for hematology parameters between the dose level groups. The ***most common TEAEs associated with hematology parameters*** (in > 10% of participants) were anaemia (13 [52.0%] participants), neutrophil count decreased (11 [44.0%] participants), thrombocytopenia (6 [24.0%] participants), neutropenia (5 [20.0%] participants) platelet count decreased (5 [20.0%] participants), and white blood cell count decreased (3 [12.0%] participants).

- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: For the majority of parameters assessed, shifts from baseline in toxicity grades indicating worsening were reported for most participants. Parameters with a higher incidence of shifts to worse toxicity grades included hemoglobin (low), leukocytes (low), lymphocytes (low) neutrophils (low), and platelets (low). There were no meaningful differences in the incidence of shifts to higher toxicity grades for hematology parameters between the dose level groups. The ***most common TEAEs associated with hematology parameters*** (in > 10% of participants) were anaemia (10 [55.6%] participants), neutrophil count decreased and platelet count decreased (7 [38.9%] participants each), neutropenia and thrombocytopenia (6 [33.3%] participants), and lymphocyte count decreased (2 [11.1%] participants).

Biochemistry

- AG-270/S95033 Monotherapy: For the majority of parameters assessed, there were a low number of shifts from baseline in toxicity grades. Parameters with a higher incidence of shifts to worse toxicity grades included ALT (high), albumin (low), blood alkaline phosphatase (ALP) [high], AST (high), bilirubin (high), creatinine (high), glucose (high), phosphate (low), potassium (low), and sodium (low). There were no meaningful differences in the incidence of shifts to higher toxicity grades for biochemical parameters between the dose level groups. The ***most common TEAEs associated with biochemical parameters*** (in > 10% of participants) were blood bilirubin increased (9 [22.5%] participants), AST increased (6 [15.0%] participants), hyperbilirubinaemia (5 [12.5%] participants), and ALT increased and hyperglycaemia (4 [10.0%] participants each).
- AG-270/S95033 in Combination With Docetaxel: For the majority of parameters assessed, there were a low number of shifts from baseline in toxicity grades. Parameters with a higher incidence of shifts to worse toxicity grades included ALT (high), albumin (low), ALP (high), AST (high), bilirubin (high), calcium (low), creatinine (high), glucose (high), magnesium (low), phosphate (low), potassium (low), and sodium (low). There were no meaningful differences in the incidence of shifts to higher toxicity grades for biochemical parameters between the dose level groups. The ***most common TEAEs associated with biochemical parameters*** (in > 10% of participants) were blood bilirubin increased (4 [16.0%] participants), hypoalbuminaemia, hyponatraemia, and hypophasphataemia (3 [12.0%] participants each).
- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: For the majority of parameters assessed, there were a low number of shifts from baseline in toxicity grades. Parameters with a higher incidence of shifts to worse toxicity grades included ALT (high), albumin (low), ALP (high), AST (high), bilirubin (high), calcium (low), creatinine (high), glucose (high), magnesium (low), phosphate (low), and potassium (low). There were no meaningful differences in the incidence of shifts to higher toxicity grades for biochemical parameters between the dose level groups. The ***most common TEAEs associated with biochemical parameters*** (in > 10% of participants) were ALT increased (7 [38.9%] participants), AST increased (6 [33.3%] participants), blood ALP increased (4 [22.2%] participants), hypokalaemia (3 [16.7%] participants), and hyperbilirubinaemia, hypoalbuminaemia, and phyophosphataemia (2 [11.1%] participants each).

Coagulation

In all treatment arms, the majority of coagulation parameter results were missing. No TEAEs associated with coagulation parameters were reported in > 10% of participants.

Other safety evaluation

Vital signs and clinical examination

One participant who received AG-270/S95033 100 mg QD + nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 had a positive urine pregnancy test at the Safety Follow-up visit.

Other observations related to safety

- AG-270/S95033 Monotherapy: All participants had an ECOG status of 0 or 1 at baseline, and the majority of post-baseline ECOG results were 0 or 1. TEAEs related to ECG findings included electrocardiogram T wave inversion (1 [2.5%] participant), tachycardia (2 [5.0%] participants), and atrial fibrillation, sinus tachycardia, and supraventricular tachycardia (1 [2.5%] participant each). TEAEs related to ophthalmological evaluations included vision blurred (2 [5.0%] participants), and optic disc haemorrhage and retinal haemorrhage (1 [2.5%] participant each).
- AG-270/S95033 in Combination With Docetaxel: All participants had an ECOG status of 0 or 1 at baseline, and the majority of post-baseline ECOG results were 0 or 1. Overall, atrial fibrillation, cardio-respiratory arrest and pericardial effusion were detected in 1 participant (4.0%), each. Overall, dry eye was detected in 2 participants (8.0%), and glaucoma and retinal degeneration in 1 participant (4.0%), each.

- AG-270/S95033 in Combination With nab-Paclitaxel and Gemcitabine: All participants had an ECOG status of 0 or 1 at baseline, and the majority of post-baseline ECOG results were 0 or 1. Overall, sinus tachycardia was detected in 1 participant (5.6%). Dry eye, photopsia, scleral disorder, vision blurred and vitreous floaters were detected in 1 participant (5.6%), each.

Conclusion:
Study enrollment was terminated in June 2022 following clinical development reassessment by the Sponsor. The decision was not taken because of concerns regarding the safety of AG-270/S95033. Overall, the safety data collected during the study indicated no new major safety concerns other than the important identified risk and were consistent with the safety profile of AG-270/S95033 known at present.

Date of the Report: 10 November 2023