# Study Results Synopsis for Public Disclosure

**Name of product:** MGY825

**Protocol identification number:** CMGY825A12101 (EU CT number: 2023-504350-36 and ClinicalTrials.gov number: NCT05275868)

**Title of study:** An open-label, phase I, dose escalation, expansion study of MGY825 in adult patients with advanced non-small cell lung cancer

**Study centers:** Study was conducted in 13 centers in 6 countries: Germany (3 centers and 8 patients), Spain (1 center and 1 patient), United States (5 centers and 23 patients), Japan (1 center and 3 patients), Switzerland (2 centers and 4 patients) and Republic of Korea (1 center and 2 patients)

**Publication (reference)**: Not applicable

**Study period:**

Study initiation date: 05-Oct-2022 (first patient first visit)

Early termination date: 13-Oct-2025

**Phase of development (phase of this clinical study):** I

**Objectives:**

This synopsis provides the results of the final safety, tolerability, efficacy and pharmacokinetics analysis with the last patient last visit (LPLV) of 13-Oct-2025.

The primary and secondary objectives and endpoints of the study are outlined in Table 2-1.

**Table 2-1 Objectives and related endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary Objective** | **Endpoints for primary objective** |
| To characterize the safety and tolerability of MGY825 in patients with non-small cell lung cancer (NSCLC) and identify the maximum tolerated dose(s) (MTD(s)) and/or recommended dose(s) (RD(s)) and dosing regimen for future studies | Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory parameters, vital signs, and electrocardiograms (ECGs)<br>Incidence and nature of dose limiting toxicities (DLTs) during the first 28 days of treatment with MGY825<br>Tolerability: Dose interruptions, reductions, and dose intensity |
| **Secondary Objectives** | **Endpoints for secondary objectives** |
| To assess the preliminary anti-tumor activity of MGY825 | Overall response rate (ORR), progression-free survival (PFS), duration of response (DOR) as per RECIST v1.1 |
| To evaluate the pharmacokinetic (PK) of MGY825 | Plasma concentration vs time profiles and derived PK parameters for MGY825 and VYR988 (e.g., Cmax, Tmax, AUC) |

**Study design and methodology:**

This was a phase I, first-in-human, open-label, multi-center study evaluating MGY825 as a single agent in adults with advanced NSCLC. The study consisted of a dose escalation part to characterize the safety and tolerability of MGY825 and identify the MTD/RD, followed by a dose expansion part to assess the preliminary anti-tumor activity in specific patient populations. Additionally, an exploratory assessment of the effect of food was planned.

For the dose escalation part of the study, a minimum of 21 patients were required to be enrolled, in cohorts of 3-6 patients. For the dose expansion part, approximately 40 patients per group were planned. The Food effect (FE) was to be evaluated in a cohort consisting of approximately up to 15 patients.

On 30-Sep-2025 Novartis decided to halt enrollment for business reasons and not due to emerging safety concerns. On 13-Oct-2025 LPLV was achieved and the study was terminated. The FE cohort and dose expansion part were not initiated.

**Diagnosis and main criteria for inclusion:**

In the dose escalation part, the study population consisted of adult patients with advanced (metastatic or unresectable) NSCLC harboring Nuclear Factor, Erythroid 2 Like 2 (NFE2L2) or Kelch-like ECH-Associated Protein 1 (KEAP1) or Cullin 3 (CUL3) mutations, for whom standard of care therapy for their indication had failed or who were intolerant of or ineligible for approved therapies.

Dose expansion Group 1 and the FE cohort, were designed to enroll the same patient population as in the dose escalation part. Dose expansion Group 2 was designed to enroll patients with advanced (metastatic or unresectable) NSCLC irrespective of NFE2L2/KEAP1/CUL3 mutational status, for whom standard of care therapy for their indication had failed or who were intolerant of or ineligible for approved therapies.

However, due to study early termination dose expansion and FE was not initiated.

Below is the list of key inclusion criteria:

- Patients must have progressed after 1 platinum-based chemotherapy regimen and PD(L)-1 antibody therapy either sequentially or concurrent with chemotherapy, where indicated, for Stage IV NSCLC
- Patients treated with neo-adjuvant / adjuvant platinum-based therapy that progressed within 6 months of treatment were permitted to participate.
- Prior therapy with VEGF/VEGFR targeting agents was permitted.
- Prior treatment with approved targeted drugs (for example EGFRi, ALKi, METi) was mandatory in patients with NSCLC whose tumor bears actionable mutations.
- Presence of at least one measurable lesion according to RECIST v1.1.

Below is the list of key exclusion criteria:

- Impaired cardiac function or clinically significant cardiac disease, or out of range laboratory values at screening.

- Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery) or increasing doses of corticosteroids 2 weeks prior to study entry. Patients with treated symptomatic brain metastases should be neurologically stable (for 4 weeks post-treatment and prior to study entry) and at a dose of ≤ 10 mg per day prednisone or equivalent for at least 2 weeks before administration of any study treatment.
- Patients treated with therapy (e.g., medications/supplements/herbs that are strong or moderate CYP3A4 inhibitors or strong or moderate CYP3A4 inducers) that cannot be discontinued 7 days prior to the start of the study and for the duration of the study.

**Test and reference therapies, dose and mode of administration**

A complete cycle of treatment was defined as 28 days of oral consumption of MGY825. MGY825 capsules were provided to the investigators at dose strength of 5 mg, 25 mg and 50 mg for oral consumption.

No reference therapy was administered.

**Protocol amendments and other changes to study conduct:**

Although the protocol was amended five times, this synopsis describes the conduct of the study according to Protocol Amendment 04 (dated 02-Apr-2024). Protocol Amendment 05 (dated 12-Aug-2024) was submitted only to the European Union to comply with European Union Clinical Trial Regulation (EU CTR) requirements and did not have an impact on the overall conduct and analyses of the study.

Summary of key changes to the protocol amendments is available in Table 2-2.

**Table 2-2 Protocol amendments**

| Version and date | Summary of key changes |
|---|---|
| **Amendment 05 (12-Aug-2024)** | To comply with the EU CTR 536/2014 the definition of study completion was amended, and trial patient data protection provisions were included. |
| **Amendment 04 (02-Apr-2024)** | • The imaging assessment collection plan was revised to include Brain computed tomography (CT) or magnetic resonance imaging (MRI) for patients with known or suspected CNS metastasis at baseline and mandated the ongoing monitoring of brain metastasis throughout the study.<br>• The eligibility criteria were updated to clarify that patients with presence of Grade ≥ 2 toxicity due to prior cancer therapy are excluded except for Grade 2 neuropathy, alopecia, skin rash that is adequately treated or endocrinopathies that are adequately treated with replacement therapy.<br>• To ensure compliance with FDA requirements, language for expedited reporting of potential Hy's Law cases was added. |
| **Amendment 03 (15-May-2023)** | • As an unexpectedly high concentration of the active metabolite of MGY825 was observed in the first patient dosed during the conduct of the trial, provisional dose levels were updated and potential exploration of a once a week (QW) MGY825 dosing regimen in the dose escalation was introduced. |

| Version and date | Summary of key changes |
|---|---|
| | • New MGY825 strengths (5 mg and 25 mg capsules) were added to provide additional dosing options. |
| **Amendment 02 (02-Nov-2022)** | The eligibility criteria modified to allow for local data confirming the NFE2L2/KEAP1/CUL3 mutation status based on liquid biopsies. |
| **Amendment 01 (13-Apr-2022)** | Health Authority requests were addressed by:<br>• Updating the study title to reflect the patient population of the study.<br>• Modifying eligibility criteria<br>  • to require prior platinum-based chemotherapy and immunotherapy either sequentially or concurrent with chemotherapy to reflect the current standard of care for patients with NSCLC.<br>  • to include patients that have progressed within 6 months of receiving adjuvant/neoadjuvant platinum-based therapy.<br>  • to exclude patients with creatinine clearance < 60 mL/min and QTcF > 470 msec.<br>• Updating the DLT criteria to exclude any death clearly due to underlying disease or extraneous causes.<br>• Revising the statistical design for each dose expansion group to implement a two-stage design. |

**Changes to the conduct of study:**

On 30-Sep-2025, Novartis decided to halt the further patient enrollment for business reasons and not due to emerging safety concerns. At the time of the enrollment halt, the dose escalation part was ongoing. The dose expansion part and FE cohort were not initiated.

**Changes in the planned analyses:**

All analyses in this report were conducted as planned in the latest version of Statistical Analysis Plan. The following changes to protocol specified analyses were applied**:**

- The Full Analysis Set (FAS) was not used for all listings of raw data. The corresponding analysis set for PK & Safety were used for listing.
- The analysis for the dose expansion part was not performed due to early termination of the study.
- PK analysis set for food effect investigation was removed due to absence of FE cohort.
- The analysis of dose proportionality and exploratory endpoints was not performed.
- Two additional PK parameters (AUCtau or AUC (0-24), VYR988/MGY825 ratio) were added in the non-compartmental PK parameter list.
- Supportive analysis for efficacy endpoints was not performed as no objective tumor responses are observed.

**Criteria for evaluation:**

**Efficacy:** Tumor response was assessed locally according to RECIST v1.1 for patients with solid tumors. The local investigator's assessment was used for the evaluation of the preliminary antitumor activity of MGY825 and for treatment decision making.

**Pharmacokinetics:** Non-compartmental PK parameters were derived for each individual plasma concentration-time profile using Phoenix WinNonlin (Version 8.3) in dose escalation. Plasma concentrations of MGY825 and its metabolite VYR988 were measured using the respective validated liquid chromatography-tandem mass spectrometry assay; the anticipated lower limit of quantification (LLOQ) was 10.0 ng/mL for MGY825 and 0.1 ng/mL for VYR988.

**Safety:** Safety assessments consisted of all AEs, along with their severity and relationship to the study drug as well as relevant findings from vital signs, height and weight, Eastern Cooperative Oncology Group (ECOG) performance status, laboratory evaluation (hematology and blood chemistry), electrocardiogram (ECG) and cardiac imaging, pregnancy and fertility, and chest X-ray.

**Statistical methods:**

**Analysis set:**

- **Full Analysis Set (FAS) and Safety Set:** included all patients who received at least one dose of study treatment.
- **Dose Determining Set (DDS):** included all FAS patients who met the minimum exposure criteria and had sufficient safety evaluations (as determined by Novartis and Investigator) or experienced a DLT during the DLT-evaluation period.
- **Pharmacokinetic Analysis Set (PAS):** included all patients who received at least one planned dose of study drug and provide at least one evaluable pharmacokinetic concentration (for MGY825 or VYR988).
- **Full Pharmacokinetic Analysis Set (FPAS):** included PAS patients with extensive PK collection schedule who had at least one evaluable PK profile. A profile was considered evaluable if the patient received the planned dose and had at least one valid primary PK parameter (for either MGY825 or VYR988).

Data were summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) by treatment group and overall patients.

**Efficacy:** Full analysis set was used for efficacy endpoints. Data collected was listed and summarized. Overall Response Rate (ORR) was calculated using 90% confidence intervals derived from the exact binomial distribution. Duration of Response (DOR) and Progression Free Survival (PFS) were summarized using Kaplan-Meier method along with 95% confidence intervals. For DOR if fewer than 5 responders were observed, Kaplan–Meier estimates were not derived; instead, only descriptive summary statistics for responder status were presented, along with event and censoring information.

**Safety:** Dose determining set was used for DLTs. Safety analysis set was used for other safety endpoints. The assessment of safety was based on the type, frequency and severity of AEs, the laboratory values that fall outside of pre-determined ranges (CTCAE V5.0 grading limits or normal ranges as appropriate) as well as clinically relevant ECG and vital sign. The dose

escalation was guided by Bayesian Hierarchical Logistic Regression Model (BHLRM) guided by the escalation with overdose control (EWOC) principle.

**Pharmacokinetics:** The PK parameters were calculated using the PK profiles of MGY825 and VYR988, separately. Full pharmacokinetic analysis set (FPAS) and pharmacokinetic analysis set (PAS) were used to summarize the PK parameters and illustrate concentration vs time profiles by treatment and visit timepoint.

## Summary - Results

**Demographic and background characteristics:**

- All 41 patients were included in the FAS and Safety Set. The DDS comprised 30 patients, while 35 patients were included in both the PAS and FPAS.
- A total of 41 patients received the study treatment. All patients discontinued the study treatment; the primary reason for study treatment discontinuation was 'progressive disease (51.2%)'.
- 27 patients (65.9%) were male and 14 were female (34.1%) with a median age of 66 years (range: 47–83 years). The majority of the patients (78.0%) were white.
- At baseline, the median weight of the patients was 77.7 kg (range: 44.7–155.3 kg). Majority of the patients had ECOG performance status 1 (80.5%) and were former smokers (85.4%) and KEAP1 mutated (73.2%).

**Protocol deviations:**

Twelve patients (29.3%) incurred protocol deviations. The most frequently reported deviations were 'missed assessments, tests, collections and/or procedures indicative of non-compliance (n=4 patients, 9.8%)' and 'SAE not reported within 24 hours of site's awareness' (n=4 patients, 9.8%).

None of the reported protocol deviations were considered to have had a significant impact on the patient's safety or the interpretations of the study results.

**Exposure:**

A total of 41 patients received at least one dose of MGY825 and were included in the safety set. The median duration of exposure was 7.1 weeks (range: 0.6–44.0 weeks) and median relative dose intensity (RDI) was 98.0% (range: 31.9–116.1).

**Efficacy results:**

Efficacy results are presented as cumulative results across all dose groups.

- No patients achieved a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR). BOR of Stable Disease (SD) was observed in 10 patients (24.4%), while progressive disease was reported in 15 patients (36.6%); 16 patients (39.0%) had a BOR that was not evaluable.
- The DOR and the corresponding Kaplan-Meier estimates were not evaluable as no patients achieved a CR or PR.
- The median PFS was 1.8 months (95% CI: 1.6, 2.9). The Kaplan-Meier estimated PFS rate at 3 months was 32.9% (95% CI: 17.0, 49.9).

**Pharmacokinetic results:**

The summary of derived PK parameters for MGY825 and the active metabolite VYR988 across the administered once-daily doses are presented in Tables 2-3 and Table 2-4.

The median time to reach maximum drug concentration of MGY825 (Tmax) was approximately between 1 and 3 hours. Increase in dose resulted in an increase in exposure (AUC, Cmax) of MGY825, with no evidence of non-proportional data trends. Upon multiple dosing, there was little to moderate accumulation [Mean Racc: C1D15/C1D1 for AUC1) ranging from ~0.9 to 2.05, observed across dose groups, which is consistent with an observed half-life of approximately 5 to 11 hours for MGY825. Similarly, VYR988 exposures increased in response to increase in doses. Tmax for VYR988 was between ~5–8 hours.

The intersubject variability was generally close to 50% or above [for AUC (0-24)] across doses and cycles for MGY825.

**Table 2-3 Summary statistics of PK parameters for MGY825 QD dose groups (Full pharmacokinetic analysis set)**

| Treatment | Statistics | AUC 0-24h (h*ng/mL) | Cmax (ng/mL) | Tmax (h) |
|---|---|---|---|---|
| **Cycle 1 Day 1** | | | | |
| MGY825 10 mg QD (N=6) | n | 5 | 6 | 6 |
| | Geo-mean | 2060 | 288 | - |
| | Geo-CV% | 55.5 | 21.0 | - |
| MGY825 20 mg QD (N=6) | n | 6 | 6 | 6 |
| | Geo-mean | 8540 | 729 | - |
| | Geo-CV% | 39.2 | 40.4 | - |
| MGY825 25 mg QD (N=11) | n | 10 | 11 | 11 |
| | Geo-mean | 9520 | 939 | - |
| | Geo-CV% | 50.0 | 43.9 | - |
| MGY825 30 mg QD (N=3) | n | 1 | 3 | 3 |
| | Geo-mean | 10100 | 748 | - |
| | Geo-CV% | NE | 104.7 | - |
| **Cycle 1 Day 15** | | | | |
| MGY825 10 mg QD (N=6) | n | 6 | 6 | 6 |
| | Geo-mean | 4140 | 461 | - |
| | Geo-CV% | 65.4 | 28.7 | - |
| MGY825 20 mg QD (N=6) | n | 2 | 2 | 2 |
| | Geo-mean | 5150 | 727 | - |
| | Geo-CV% | 84.2 | 0.8 | - |
| MGY825 25 mg QD (N=11) | n | 4 | 4 | 4 |
| | Geo-mean | 12400 | 1320 | - |
| | Geo-CV% | 48.2 | 22.2 | - |
| MGY825 30 mg QD (N=3) | n | 1 | 1 | 1 |
| | Geo-mean | 12600 | 835 | - |
| | Geo-CV% | NE | NE | - |

**Table 2-4 Summary statistics of PK parameters for VYR988 QD dose groups (Full pharmacokinetic analysis set)**

| Treatment | Statistics | AUC 0-24h (h*ng/mL) | Cmax (ng/mL) | Tmax (h) | VYR988/MGY825 ratio (%) |
|---|---|---|---|---|---|
| **Cycle 1 Day 1** | | | | | |
| MGY825 10 mg QD (N=6) | n | 4 | 6 | 6 | 4 |
| | Geo-mean | 47.5 | 4.36 | - | 2.55 |
| | Geo-CV% | 81.5 | 73.4 | - | 18.8 |
| MGY825 20 mg QD (N=6) | n | 4 | 6 | 6 | 4 |
| | Geo-mean | 297 | 16.2 | - | 3.40 |
| | Geo-CV% | 50.4 | 58.0 | - | 28.4 |
| MGY825 25 mg QD (N=11) | n | 7 | 11 | 11 | 7 |
| | Geo-mean | 215 | 17.9 | - | 2.51 |
| | Geo-CV% | 67.0 | 52.5 | - | 35.5 |
| MGY825 30 mg QD (N=3) | n | 2 | 3 | 3 | 2 |
| | Geo-mean | 403 | 17.9 | - | 2.86 |
| | Geo-CV% | 20.2 | 81.1 | - | 28.0 |
| **Cycle 1 Day 15** | | | | | |
| MGY825 10 mg QD (N=6) | n | 6 | 6 | 6 | 6 |
| | Geo-mean | 92.2 | 6.62 | - | 2.23 |
| | Geo-CV% | 80.0 | 80.3 | - | 89.8 |
| MGY825 20 mg QD (N=6) | n | 1 | 3 | 3 | 1 |
| | Geo-mean | 99.0 | 15.0 | - | 3.22 |
| | Geo-CV% | NE | 44.4 | - | NE |
| MGY825 25 mg QD (N=11) | n | 3 | 4 | 4 | 3 |
| | Geo-mean | 598 | 35.4 | - | 4.14 |
| | Geo-CV% | 76.6 | 64.6 | - | 27.3 |
| MGY825 30 mg QD (N=3) | n | 1 | 1 | 1 | 1 |
| | Geo-mean | 1140 | 64.5 | - | 9.06 |
| | Geo-CV% | NE | NE | - | NE |

**Safety results:**

Safety results are presented as cumulative results across all dose groups.

**Incidence of Adverse Events Regardless of Study Treatment Relationship**

- Overall, 40 out of 41 patients (97.6%) experienced at least one AE regardless of study drug relationship. AEs by SOC that occurred most frequently were gastrointestinal disorders (n=33 patients, 80.5%), general disorders and administration site conditions (n=24 patients, 58.5%), and metabolism and nutrition disorders (n=23 patients, 56.1%).
- The most frequently reported AEs by PT (≥ 20%) across all doses were nausea (n=23 patients, 56.1%), vomiting (n=19 patients, 46.3%), diarrhea (n=17 patients, 41.5%),

fatigue (n=16 patients, 39.0%), dyspnea (n=12 patients, 29.3%) and decreased appetite (n=9 patients, 22.0%).

- Grade ≥ 3 AEs were reported in 29 patients (70.7%) and the most frequently reported Grade ≥ 3 AEs by PT (≥ 5 %) were anemia, platelet count decreased, pneumonia (n=4 patients, 9.8% each), stomatitis, infection, back pain, tumor pain, and hypophosphatemia (n=3 patients, 7.3% each).

**Dose-Limiting Toxicities**

A total of 30 (73.2%) patients were included in dose determining analysis set. DLTs were reported in 9 patients (30.0%), of whom 8 patients (26.7%) experienced at least one Grade ≥3 DLT. The majority of DLTs were Grade ≥3 severity.

The most frequently reported DLTs by PT were stomatitis (n=3 patients,10.0%), all of which were Grade ≥ 3, followed by fatigue (n=2 patients, 6.7%), of which 1 patient (3.3%) had Grade ≥ 3 fatigue. All other DLTs were reported in 1 patient each (3.3%), including anemia, hypokalemia, hypophosphatemia, mucosal inflammation, platelet count decreased (Grade ≥ 3) disturbance in attention, and encephalopathy (both Grade 2).

**Determination of MTD/RD**

Due to limited data and enrollment halt leading to early termination of the study, MTD/RD was not declared.

**Treatment-related Adverse events**

- A total of 35 patients (85.4%) experienced at least one treatment-related adverse event (TRAE). The most frequently reported TRAEs by PT (all grades, ≥ 20%) were nausea (n=20 patients, 48.8%), vomiting (n=17 patients, 41.5%), diarrhea (n=14 patients, 34.1%), decreased appetite and fatigue (n=9 patients, 22.0% each) (Table 2-5).
- Grade ≥ 3 TRAEs by PT (≥ 5%) were reported in 15 patients (36.6%). The most frequently reported Grade ≥3 TRAEs included platelet count decreased (n=4 patients, 9.8%), stomatitis, hypophosphatemia and anemia (n=3 patients, 7.3% each).

**Serious adverse events**

- Overall, 28 patients (68.3%) experienced SAEs, regardless of study drug relationship.
- Treatment-related SAEs (TRSAEs) were reported in 9 patients (22.0%), of whom 7 patients (17.1%) experienced Grade ≥ 3 TRSAEs. The most frequently reported TRSAEs by PT (all grades, ≥ 2.5% patients) were diarrhea, nausea and vomiting (n=2 patients, 4.9% each) (Table 2-6).
- The Grade ≥ 3 TRSAEs reported were diarrhea, nausea, vomiting, cerebrovascular accident, mucosal inflammation, nervous system disorder, pancreatitis, platelet count decreased, and stomatitis (n=1 patient, 2.4% each).

**Table 2-5 AEs suspected to be study treatment related by PT (≥ 5 % all grades, all patients) and severity (Safety set)**

| | MGY825 10 mg QD N=6 | | MGY825 20 mg QD N=6 | | MGY825 25 mg QD N=12 | | MGY825 30 mg QD N=4 | | MGY825 100 mg QD N=1 | | MGY825 30 mg 1/1* N=6 | | MGY825 50 mg QW N=6 | | All Patients N=41 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Preferred term | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) | All grades n (%) | Grade >=3 n (%) |
| Number of patients with at least one event | 4 (66.7) | 1 (16.7) | 5 (83.3) | 1 (16.7) | 10 (83.3) | 6 (50.0) | 4 (100) | 3 (75.0) | 1 (100) | 0 | 5 (83.3) | 3 (50.0) | 6 (100) | 1 (16.7) | 35 (85.4) | 15 (36.6) |
| Nausea | 2 (33.3) | 0 | 3 (50.0) | 0 | 5 (41.7) | 0 | 3 (75.0) | 1 (25.0) | 1 (100) | 0 | 2 (33.3) | 0 | 4 (66.7) | 0 | 20 (48.8) | 1 (2.4) |
| Vomiting | 1 (16.7) | 0 | 2 (33.3) | 0 | 6 (50.0) | 1 (8.3) | 2 (50.0) | 0 | 1 (100) | 0 | 3 (50.0) | 0 | 2 (33.3) | 0 | 17 (41.5) | 1 (2.4) |
| Diarrhoea | 1 (16.7) | 0 | 1 (16.7) | 0 | 3 (25.0) | 1 (8.3) | 2 (50.0) | 0 | 1 (100) | 0 | 3 (50.0) | 0 | 3 (50.0) | 1 (16.7) | 14 (34.1) | 2 (4.9) |
| Decreased appetite | 2 (33.3) | 0 | 1 (16.7) | 0 | 2 (16.7) | 0 | 1 (25.0) | 0 | 1 (100) | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 9 (22.0) | 0 |
| Fatigue | 1 (16.7) | 0 | 3 (50.0) | 1 (16.7) | 1 (8.3) | 0 | 2 (50.0) | 1 (25.0) | 0 | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 9 (22.0) | 2 (4.9) |
| Stomatitis | 0 | 0 | 1 (16.7) | 0 | 1 (8.3) | 0 | 2 (50.0) | 2 (50.0) | 1 (100) | 0 | 3 (50.0) | 1 (16.7) | 0 | 0 | 8 (19.5) | 3 (7.3) |
| Platelet count decreased | 0 | 0 | 0 | 0 | 0 | 0 | 4 (100) | 2 (50.0) | 1 (100) | 0 | 2 (33.3) | 2 (33.3) | 0 | 0 | 7 (17.1) | 4 (9.8) |
| Anaemia | 0 | 0 | 1 (16.7) | 0 | 1 (8.3) | 1 (8.3) | 3 (75.0) | 1 (25.0) | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 | 0 | 6 (14.6) | 3 (7.3) |
| Lipase increased | 0 | 0 | 1 (16.7) | 0 | 2 (16.7) | 1 (8.3) | 0 | 0 | 1 (100) | 0 | 0 | 0 | 1 (16.7) | 0 | 5 (12.2) | 1 (2.4) |
| Thrombocytopenia | 2 (33.3) | 1 (16.7) | 1 (16.7) | 1 (16.7) | 1 (8.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 (9.8) | 2 (4.9) |
| Weight decreased | 0 | 0 | 0 | 0 | 2 (16.7) | 0 | 1 (25.0) | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 4 (9.8) | 0 |
| Dry mouth | 1 (16.7) | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (25.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (7.3) | 0 |
| Dry skin | 1 (16.7) | 0 | 0 | 0 | 1 (8.3) | 0 | 1 (25.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (7.3) | 0 |
| Hyperglycaemia | 1 (16.7) | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 3 (7.3) | 1 (2.4) |

| | MGY825 10 mg QD N=6 | | MGY825 20 mg QD N=6 | | MGY825 25 mg QD N=12 | | MGY825 30 mg QD N=4 | | MGY825 100 mg QD N=1 | | MGY825 30 mg 1/1* N=6 | | MGY825 50 mg QW N=6 | | All Patients N=41 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 |
| **Preferred term** | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Hypophosphataemia | 0 | 0 | 1 (16.7) | 1 (16.7) | 1 (8.3) | 1 (8.3) | 1 (25.0) | 1 (25.0) | 0 | 0 | 0 | 0 | 0 | 0 | 3 (7.3) | 3 (7.3) |
| Neutropenia | 0 | 0 | 0 | 0 | 1 (8.3) | 0 | 1 (25.0) | 0 | 0 | 0 | 1 (16.7) | 1 (16.7) | 0 | 0 | 3 (7.3) | 1 (2.4) |
| Rash | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 2 (50.0) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 (7.3) | 0 |

*1/1: 1 week on/ 1 week off QD
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 28.1, CTCAE version V5.0.

**Table 2-6 SAEs suspected to be study treatment related by PT (≥ 2.5 % all grades, all patients) and severity (Safety set)**

| | MGY825 10 mg QD N=6 | | MGY825 20 mg QD N=6 | | MGY825 25 mg QD N=12 | | MGY825 30 mg QD N=4 | | MGY825 100 mg QD N=1 | | MGY825 30 mg 1/1* N=6 | | MGY825 50 mg QW N=6 | | All Patients N=41 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 | All grades | Grade >=3 |
| **Preferred term** | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Number of patients with at least one event | 1 (16.7) | 1 (16.7) | 0 | 0 | 5 (41.7) | 3 (25.0) | 1 (25.0) | 1 (25.0) | 0 | 0 | 2 (33.3) | 2 (33.3) | 0 | 0 | 9 (22.0) | 7 (17.1) |
| Diarrhoea | 0 | 0 | 0 | 0 | 1 (8.3) | 1 (8.3) | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 2 (4.9) | 1 (2.4) |
| Nausea | 0 | 0 | 0 | 0 | 1 (8.3) | 0 | 1 (25.0) | 1 (25.0) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4.9) | 1 (2.4) |
| Vomiting | 0 | 0 | 0 | 0 | 2 (16.7) | 1 (8.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4.9) | 1 (2.4) |

*1/1: 1 week on/ 1 week off QD
Numbers (n) represent counts of patients.
A patient with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 28.1, CTCAE version V5.0.

**Adverse events leading to discontinuation**

- A total of 6 patients (14.6%) discontinued study treatment due to AEs, regardless of study treatment relationship. Of these, 5 patients (12.2%) reported Grade ≥ 3 AEs .
- The Grade ≥ 3 AEs leading to discontinuation were diarrhea, pancreatitis, stomatitis, cerebrovascular accident, and hypotension (n=1 patient, 2.4% each).

**Dose Reductions or interruptions**

Five patients (12.2%) required at least one dose reduction due to AE. At least one dose interruption due to AE was reported in 29 patients (70.7%).

**AEs requiring additional therapy**

Additional therapy for AEs regardless of causality was required by 39 patients (95.1%) .

**On-treatment Deaths**

Seven deaths (17.1%) occurred while patients were on treatment across different dosage groups. The majority of deaths (6 patients; 14.6%) were attributed to progression of the underlying malignancy (study indication). One patient (2.4%) from MGY825 25 mg once daily (QD) group died due to a fatal SAE - cerebrovascular accident (CVA), which was suspected to be related to study-treatment. As per the investigator, the CVA event is more commonly observed in association with Trousseau syndrome, which is a paraneoplastic condition. However, due to the close temporal relationship, the causality of the adverse event CVA with MGY825 could not be ruled out.

**Clinical laboratory evaluation**

*Hematology*

The most frequently reported Grade 3/4 post-baseline hematology abnormalities included platelets decrease (n=6 patients, 14.6%) and hemoglobin decrease (n=5 patients, 12.2%). Leukocytes decrease, and neutrophils decrease were each reported in 1 patient (2.4%).

*Biochemistry*

The most frequently reported Grade 3/4 post-baseline biochemistry abnormalities included gamma-glutamyl transferase increased (n=7 patients, 17.1%) and lipase increased (n=5 patients, 12.2%). Albumin decreased, alkaline phosphatase increased, amylase increased, and creatinine increased were each reported in 1 patient (2.4%).

*Liver Enzymes*

ALT or AST > 3x ULN was the only one reported worst post-baseline hepatic laboratory value (n=1 patient, 2.4%). There were no potential Hy's Law cases reported.

**Vital signs**

Among 41 patients across all dose groups, the majority of the patients did not have a notable change in vital sign values. The most common notable vital sign values were

pulse rate ≥ 100 bpm with > 25% increase from baseline (n=8 patients, 19.5%), systolic BP ≤ 90 mmHg with ≥ 20 mmHg decrease from baseline (n=5 patients, 12.2%), ≥ 10% weight decrease from baseline (n=4 patients, 9.8%) and diastolic BP ≤ 50 mmHg with ≥15 mmHg decrease from baseline (n=2 patients, 4.9%).

**Electrocardiogram**

Among 39 patients (excluding 2 patients without baseline value) across all dose groups, increase in QTcF from baseline of > 30 to ≤ 60 ms was observed in 6 patients (15.4%). No patients experienced QTcF increase from baseline > 60 ms. No new QTcF values > 500 ms, were observed in any patient across all dose groups.

No clinically significant trends in vital signs and ECG were observed during the on-treatment period.

## Conclusions:

Based on the overall evaluation of safety data from Study CMGY825A12101the observed safety profile of MGY825 was considered manageable. No unexpected safety signals were identified during the conduct of the study.

Systemic exposure (AUC(0–24h) and Cmax) for MGY825 increased with dose following QD administration, with Tmax typically occurring within ~1–3 hours. Moderate accumulation was observed at steady state (Racc ~1–2), indicating limited drug accumulation with repeated dosing. Tmax for VYR988 was between ~5–8 hours, consistent with metabolite formation kinetics.

With respect to efficacy, no objective tumor responses were observed.

The decision to terminate the development program for MGY825 was made by Novartis for business reasons and was not driven by emerging safety concerns from this study or the overall safety dataset.