Phase I Trial of a Third Generation EGFR Mutant-Selective Inhibitor (D-0316) in Patients with Advanced Non-Small Cell Lung Cancer

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Abstract

Background: D-0316 is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) developed for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR T790M mutation that progressed after prior treatment with the first- or second-generation EGFR-TKI.

Methods: This phase I, open-label, multicenter clinical trial evaluated daily oral D-0316 administration in dose-escalation (25 to 150 mg; 17 patients) and dose-expansion (50, 100 mg; 67 patients) cohorts for safety, tolerability, anti-tumor activity, and pharmacokinetics.

Results: D-0316 was well tolerated at daily doses of 25 to 150 mg and the maximum tolerated dose (MTD) was not reached. The most common treatment-related adverse events (AEs) were platelet count decreased, electrocardiogram QT corrected interval prolonged, anemia, rash, low white blood cell count, hypertriglyceridemia, high cholesterol, headache, pruritus, cough, and aspartate transaminase (AST) or alanine transaminase (ALT) increased. Most of AEs were grade 1 or 2. In the 50 and 100 mg group, the overall response rate (ORR) was 33.3% and 45.5%, the disease control rate (DCR) was 86.7% and 93.9%, and the median PFS was 8.3 and 9.6 months, respectively. D-0316 exposure increased in proportion to dose from 25 to 150 mg. The recommended phase II dose (RP2D) was 100 mg.

Conclusion: D-0316 is safe, tolerable, and effective for patients with locally advanced/metastatic NSCLC with the EGFR T790M mutation who previously received EGFR-TKI.

ClinicalTrials.gov Identifier: NCT03452150.

Key words: epidermal growth factor receptor; EGFR T790M mutation; non-small cell lung cancer (NSCLC); phase I; efficacy; safety

Lessons Learned

- D-0316 is an orally available irreversible third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) that overcomes resistance mechanisms of the first- and second-generation EGFR TKIs.
- D-0316 is safe, tolerable, and apparently effective for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that carries T790M mutation.

Discussion

The first- and second-generation EGFR TKIs are now used worldwide to treat advanced NSCLC; however, patients taking these drugs develop different degrees of acquired drug resistance and need to switch to new treatments. The present study was a first-in-human phase I study to evaluate the safety, efficacy, and pharmacokinetics (PK) of D-0316 in patients with advanced NSCLC.

Our results showed that D-0316 was well tolerated at daily doses ranging from 25 to 150 mg and effectively controlled disease at 50 and 100 mg dose levels. At dose levels tested, D-0316 exposure increased with the dose proportionally with an apparent linear correlation, consistent with other third-generation EGFR-TKIs.1,2

Only one dose-limiting toxicity occurred in a patient who received a 100 mg dose, and the MTD was not reached.
The low rate of grade 3 or higher drug-related rash (0%), maculopapular rash (1.2%), and diarrhea (0%) was remarkably different from that observed in osimertinib studies, presumably due to the successful molecular design of D-0316 to block the formation of a key metabolite that is active against wild-type EGFR. Thus, the safety profile of D-0316 appeared to be different from other EGFR-TKIs, in that the occurrence of rash, maculopapular rash, and diarrhea was significantly lower (34.5%, 1.2%, and 6.0%, respectively).

Efficacy results of D-0316 are shown in Figure 1. The ORR of the 50 mg expansion dose group was 33.3% and that of the 100 mg expansion was 45.5%, and the DCR in 50 mg group (86.7%) was lower than in 100 mg group (93.9%). The efficacy in the 100 mg group is clinically significant, especially considering that 75.0% of patients in this group had extrathoracic metastases. More than 50% of patients in expansion groups had received more than one prior EGFR TKI or chemotherapy treatment, suggesting that D-0316 can be effective despite multiple lines of prior treatment.

The efficacy results from this study are comparable to other third-generation EGFR TKIs’ early phase study results and warrant further evaluation in a larger population.

The phase II extension of the present study uses a 100-mg QD regimen and is ongoing (NCT03861156). In addition, a randomized, open-label, multicenter, phase III study is currently assessing the efficacy and safety of D-0316 versus Icotinib as a first-line treatment for patients with EGFR mutation-positive, locally advanced or metastatic NSCLC (NCT04206072). These two trials will also include more detailed analyses of patients with brain metastases.

In summary, D-0316 is a third-generation irreversible TKI that is safe, tolerable, and apparently effective for patients who have locally advanced or metastatic NSCLC with EGFR T790M mutation and who previously received a first- or second-generation EGFR-TKI. Further development of D-0316 may provide patients with EGFR-mutated NSCLC with a viable option for treatment.

Figure 1. Efficacy results of D-0316. (a) Changes of tumor lesion size of patients in the 50 mg and 100 mg expansion groups (waterfall plot). (b) Kaplan–Meier curves of PFS in the 50 and 100 mg expansion groups.

Author disclosures and references available online.
**Trial Information**

| Disease               | Lung cancer—NSCLC          |
|-----------------------|---------------------------|
| Stage of disease/treatment | Metastatic/advanced       |
| Prior therapy         | 1 prior regimen           |
| Type of study         | phase I, dose escalation + dose expansion |
| Primary Endpoints     | Safety, Tolerability, Maximum tolerated dose |
| Secondary Endpoints   | Recommended phase II dose, PK, Preliminary efficacy |
| Investigator's Analysis | Active and should be pursued further |

**Additional Details of Endpoints or Study Design**

The study included a dose-escalation phase to determine the MTD, and a subsequent dose-expansion phase to establish the recommended phase II dose (RP2D). The first dose escalation used an accelerated escalation scheme with one patient because of the low possibility of toxicity at this low dose. Subsequent dose escalations were conducted using a 3 + 3 design. Dose-limiting toxicities (DLT) were evaluated after the first cycle completed. Radiological examinations were performed every 6 weeks after treatment initiation for efficacy assessment.

**Drug Information: Dose Escalation, D-0316**

| Generic/working name | D-0316                              |
|----------------------|-------------------------------------|
| Drug type            | Small molecule                      |
| Drug class           | EGFR                                |
| Dose                 | 25, 50, 75, 100, and 150 mg per flat dose |
| Route                | oral (p.o.)                         |

**Dose Escalation Table**

| Dose level | Dose of drug: D-0316 | Number enrolled | Number evaluable for toxicity |
|------------|----------------------|-----------------|------------------------------|
| 25         | 1                    | 1               | 1                            |
| 50         | 2                    | 34              | 34                           |
| 75         | 3                    | 4               | 4                            |
| 100        | 4                    | 42              | 42                           |
| 150        | 5                    | 3               | 3                            |

**Drug Information: Dose Expansion, D-0316, 50 mg**

| Generic/working name | D-0316                              |
|----------------------|-------------------------------------|
| Drug type            | Small molecule                      |
| Drug class           | EGFR                                |
| Dose                 | 50 mg per flat dose                 |
| Route                | oral (p.o.)                         |

**Drug Information: Dose Expansion, D-0316, 100 mg**

| Generic/working name | D-0316                              |
|----------------------|-------------------------------------|
| Drug type            | Small molecule                      |
| Drug class           | EGFR                                |
| Dose                 | 100 mg per flat dose                |
| Route                | oral (p.o.)                         |

**Schedule of administration**

Patients received D-0316 once daily under fasting conditions in each 21-day cycle. A washout period of 7 days was set after the first day of D-0316 admission to collect PK samples.

**Schedule of administration**

Patients received D-0316 once daily under fasting conditions in each 21-day cycle. Only part of the 100 mg group patients achieved a washout period of 7 days after the first day of D-0316 admission to collect PK samples.
### Drug Information: D-0316, Total

| Generic/working name | D-0316 |
|----------------------|--------|
| Drug type            | Small molecule |
| Drug class           | EGFR |
| Dose                 | 25, 50, 75, 100, and 150 mg per flat dose |
| Route                | oral (p.o.) |
| Schedule of administration | Patients received D-0316 once daily under fasting conditions in each 21-day cycle. Only dose escalation and part of the 100 mg group patients achieved a washout period of 7 days after the first day of D-0316 admission to collect PK samples. |

### Patient Characteristics: Dose Escalation

#### Number of patients, male 8

#### Number of patients, female 9

| Stage  | M1a: n = 6 | M1b: n = 2 | M1c: n = 9 |
|--------|------------|------------|------------|

#### Age Median (range): 60 (37-74) years

| Number of prior systemic therapies | Median (range): at least one prior EGFR TKI therapy |
|------------------------------------|------------------------------------------|

#### Performance status: ECOG

| 0—6 | 1—11 | 2—0 | 3—0 | Unknown—0 |

#### Cancer types or histologic subtypes Adenocarcinoma 17

### Patient Characteristics: Dose Expansion, 50 mg

#### Number of patients, male 11

#### Number of patients, female 20

| Stage  | M1a: n = 5 | M1b: n = 5 | M1c: n = 21 |
|--------|------------|------------|-------------|

#### Age Median (range): 61 (49-75) years

| Number of prior systemic therapies | Median (range): at least one prior EGFR TKI therapy |
|------------------------------------|------------------------------------------|

#### Performance status: ECOG

| 0—10 | 1—21 | 2—0 | 3—0 | Unknown—0 |

#### Cancer types or histologic subtypes Adenocarcinoma, 29; squamous carcinoma, 1; other, 1

### Patient Characteristics: Dose Expansion, 100 mg

#### Number of patients, male 13

#### Number of patients, female 23

| Stage  | M1a: n = 9 | M1b: n = 1 | M1c: n = 26 |
|--------|------------|------------|-------------|

#### Age Median (range): 60.5 (34–75) years

| Number of prior systemic therapies | Median (range): at least one prior EGFR TKI therapy |
|------------------------------------|------------------------------------------|

#### Performance status: ECOG

| 0—6 | 1—29 | 2—1 | 3—0 | Unknown—0 |

#### Cancer types or histologic subtypes Adenocarcinoma, 36
### Patient Characteristics: Total

| Description                                | Value   |
|--------------------------------------------|---------|
| Number of patients, male                   | 32      |
| Number of patients, female                 | 52      |
| Stage                                      |         |
| M1a: n = 20                                |         |
| M1b: n = 8                                 |         |
| M1c: n = 56                                |         |
| Age Median (range): 61 (34–75) years       |         |
| Performance status: ECOG                   |         |
| 0—22                                       |         |
| 1—61                                       |         |
| 2—1                                        |         |
| 3—0                                        |         |
| Unknown—0                                  |         |
| Cancer types or histologic subtypes        |         |
| Adenocarcinoma, 82; squamous carcinoma, 1; other, 1 |

### Secondary Assessment Method for: Dose Expansion, 50 mg

| Title                                      | Tumor response |
|--------------------------------------------|----------------|
| Number of patients screened                | 155            |
| Number of patients enrolled                | 31             |
| Number of patients evaluable for toxicity  | 31             |
| Number of patients evaluated for efficacy  | 30             |
| Evaluation method                          | RECIST 1.1     |
| Response assessment PR                     | n = 10 (33.3%) |
| Response assessment SD                     | n = 16 (53.3%) |
| Response assessment PD                     | n = 4 (13.3%)  |
| (Median) duration assessments PFS          | 8.3 months, CI: 5.6-18.0 |

### Secondary Assessment Method: Dose Expansion, 100 mg

| Title                                      | Tumor response |
|--------------------------------------------|----------------|
| Number of patients screened                | 155            |
| Number of patients enrolled                | 36             |
| Number of patients evaluable for toxicity  | 36             |
| Number of patients evaluated for efficacy  | 33             |
| Evaluation method                          | RECIST 1.1     |
| Response assessment CR                     | n = 15 (45.5%) |
| Response assessment SD                     | n = 16 (48.5%) |
| Response assessment PD                     | n = 2 (6.1)    |
| (Median) duration assessments PFS          | 9.6 months, CI: 6.9-not reached |

### Primary Assessment Method, Total

| Title                                      | Safety |
|--------------------------------------------|--------|
| Number of patients screened                | 187    |
| Number of patients enrolled                | 84     |
| Number of patients evaluable for toxicity  | 84     |
| Number of patients evaluated for efficacy  | 63     |
| Evaluation method                          | CTCAE 4.03 |
### Adverse Events, All Dose Levels/All Cycles, Total

| Name                                      | -NC/NA | 1    | 2    | 3    | 4    | 5    | All grades |
|-------------------------------------------|--------|------|------|------|------|------|------------|
| Platelet count decreased                  | 43%    | 26%  | 23%  | 7%   | 1%   | 0%   | 57%        |
| Electrocardiogram QT corrected interval   | 57%    | 36%  | 6%   | 1%   | 0%   | 0%   | 43%        |
| Anemia                                    | 67%    | 29%  | 4%   | 1%   | 0%   | 0%   | 33%        |
| Rash                                      | 68%    | 32%  | 0%   | 0%   | 0%   | 0%   | 32%        |
| White blood cell decreased                | 82%    | 14%  | 4%   | 0%   | 0%   | 0%   | 18%        |
| Hypertriglyceridemia                      | 83%    | 12%  | 2%   | 2%   | 0%   | 0%   | 17%        |
| Cholesterol high                          | 83%    | 15%  | 1%   | 0%   | 0%   | 0%   | 17%        |
| Headache                                  | 85%    | 13%  | 1%   | 0%   | 0%   | 0%   | 15%        |
| Pruritus                                  | 87%    | 13%  | 0%   | 0%   | 0%   | 0%   | 13%        |
| Cough                                     | 88%    | 8%   | 4%   | 0%   | 0%   | 0%   | 12%        |
| Aspartate aminotransferase increased      | 88%    | 12%  | 0%   | 0%   | 0%   | 0%   | 12%        |
| Alanine aminotransferase increased        | 89%    | 10%  | 1%   | 0%   | 0%   | 0%   | 11%        |

Adverse events occurring in ≥10% of patients are shown.  

*NC/NA, no change from baseline/no adverse event.

### Dose-Limiting Toxicities: Dose Expansion

| Dose level | Dose of drug: D-0316 | Number enrolled | Number evaluable for toxicity | Number with a dose-limiting toxicity | Dose-limiting toxicity information |
|------------|----------------------|-----------------|-------------------------------|--------------------------------------|-----------------------------------|
| 1          | 25                   | 1               | 1                             | 0                                    |                                   |
| 2          | 50                   | 34              | 34                            | 0                                    |                                   |
| 3          | 75                   | 4               | 4                             | 0                                    |                                   |
| 4          | 100                  | 42              | 42                            | 1                                    |                                   |
| 5          | 150                  | 3               | 3                             | 0                                    |                                   |

### Dose-Limiting Toxicities: Total

| Dose of drug: D-0316 | Number evaluated for toxicity | Number with dose-limiting toxicity | Dose-limiting toxicity |
|----------------------|-------------------------------|-----------------------------------|------------------------|
| 25                   | 1                             | 0                                 | Grade 3 headache       |
| 50                   | 3                             | 0                                 |                        |
| 75                   | 4                             | 0                                 |                        |
| 100                  | 4                             | 1                                 |                        |
| 150                  | 3                             | 0                                 |                        |

### Pharmacokinetics/Pharmacodynamics: Total

| Dose level | Dose of drug: D-0316, mg | Number enrolled | C\text{max} (nmol/L), GeoMean | T\text{max} (h) median | AUC\text{0-24} (h x nmol/L), GeoMean | T\text{1/2} (h) mean | Accumulation ratio, Geomean |
|------------|--------------------------|-----------------|-----------------------------|------------------------|-------------------------------------|-------------------|-----------------------------|
| Single dose| 25                       | 1               | 79                          | 4                      | 1300                                | 48                | 48                          |
| Single dose| 50                       | 3               | 165                         | 4                      | 2750                                | 47                | 47                          |
| Single dose| 75                       | 4               | 177                         | 6                      | 2720                                | 94                | 94                          |
| Single dose| 100                      | 14              | 370                         | 4                      | 5600                                | 77                | 77                          |
| Single dose| 150                      | 3               | 346                         | 4                      | 5200                                | 95                | 95                          |
| Cycle 1 Day 15| 25                     | 1               | 292                         | 4                      | 5730                                | 4.4               | 4.4                         |
| Cycle 1 Day 15| 50                     | 31              | 570                         | 4                      | 11 100                               | 5.1               | 5.1                         |
| Cycle 1 Day 15| 75                     | 3               | 986                         | 4                      | 18 400                               | 6.5               | 6.5                         |
| Cycle 1 Day 15| 100                    | 30              | 1230                        | 4                      | 23 400                               | 4.5               | 4.5                         |
| Cycle 1 Day 15| 150                    | 3               | 1380                        | 4                      | 25 700                               | 4.9               | 4.9                         |

### Assessment, Analysis, and Discussion

Completion: Study completed  
Investigator’s Assessment: Active and should be pursued further
The present study is the first-in-human phase I study to evaluate the safety, efficacy, and PK of D-0316 in patients with advanced NSCLC. Our results showed that D-0316 was well tolerated at daily doses ranging from 25 to 150 mg and the MTD was not reached. The safety profile of D-0316 appeared to be different from other EGFR-TKIs, in that the occurrence of rash and diarrhea was significantly lower (34.5% and 6.0%, respectively). In the FLAURA study of osimertinib, rash and diarrhea both occurred in 58% of patients. Clinical trials evaluating the safety of other third-generation EGFR-TKIs (nazartinib and AC0010) also reported rash at a frequency of 62% and 48%, respectively, and diarrhea at a frequency of 45% and 75%, respectively, as the most common AEs. In the present study, we observed platelet count decreased (57%, 48/84), electrocardiogram QT corrected interval prolonged (45%, 38/84), and anemia (45%, 38/84) as the most common AEs from D-0316 treatment. The incidences of these AEs are similar in each dose group, suggesting no dose-effect correlation. Most of these events are grade 1 or 2, with grade 3 platelet count decreased occurred in 8.3% of patients (7/84; 2 in 50 mg and 5 in 100 mg group) and grade 3 electrocardiogram QT corrected interval prolonged and anemia occurred in only one patient each. Most QT interval prolongations were observed in only one ECG measurement and not confirmed by another measurement. All these events recovered without study drug dose interruption or discontinuation. It was noted that the incidence of QT interval prolongation was much lower in another phase 2 study of D-0316 where confirmatory ECGs were performed. There have been some hematological AEs observed with other EGFR-TKIs, such as anemia reported in 59% of the FLAURA study population and 43% of the AURA3 study population, and platelet count decreased reported in 51% of the FLAURA study population and 46% of the AURA3 study population in osimertinib-treated patients. Platelet count decrease was also reported as the major AE in another third-generation EGFR-TKI, TAS-121, with an occurrence of 67.2% of all grades and 13.4% of grade 3 or higher. The exact mechanism of hematological toxicity caused by EGFR-TKI is unclear, but in our current study these events were mostly mild to moderate in severity or manageable with appropriate dose modification without the need to discontinue study treatments. Another noteworthy AE in the present study is headache, which occurred in 26.2% patients (22/84), and the only DLT observed during this study was a grade 3 headache (1.2%). Except for this case, all other headaches were grade 1 or 2. The occurrence of headache in the present study seemed to be higher than that in FLAURA study, which reported 12% for any grade headache and 0.4% for grade 3 or higher. The mechanism of headache in our study is unknown but it may be related to relatively high level of central nervous system penetration by study drug D-0316.

Besides osimertinib, which is approved in many countries for the treatment of NSCLC with T790M mutation, there are other third-generation EGFR TKIs in active clinical development. Further comparison of the safety and efficacy between these EGFR TKIs and D-0316 needs to be explored in the future. Based on the reported results of osimertinib, its ORR in T790M+ patients reached 61%, which seems to be higher than D-0316 ORR in the present study (45.5% in 100 mg group). However, only 52% of patients in the osimertinib study had extra thoracic metastases, while in the present study, we had 75.0% of patients with extra thoracic metastases. Furthermore, more than half of the current study population in our expansion groups had received more than one prior EGFR TKI or chemotherapy treatment, suggesting that D-0316 may still be effective despite multiple lines of prior treatment. The high tolerability and promising efficacy result of D-0316 warrants further clinical development to potentially provide patients with T790M-mutated NSCLC an additional choice of treatment, especially in areas where osimertinib is not approved or in patients with poor tolerance to osimertinib.

Animal studies reported that oral administration of D-0316 led to significant concentrations in brain tissue with a brain/plasma concentration ratio of 12.6, which indicated the potential of D-0316 to cross the blood–brain barrier. Five of our patients had measurable intracranial lesions at baseline, and one patient achieved PR of this lesion (Figure 2). Twenty-five patients had non-measurable brain lesions, only eight (32%) of them experienced progression. During the treatment of D-0316, no patients with intracranial lesions had ever received radiotherapy. This is consistent with our observation that most patients in the expansion groups did not have disease progression in the brain and suggests that D-0316 may inhibit intracranial lesions. The efficacy of D-0316 on brain metastasis needs further evaluation in a prospective study of patients with advanced NSCLC and measurable intracranial lesions.

At dose levels tested, D-0316 exposure increased with the dose proportionally with an apparent linear correlation (Figure 3). Our efficacy data suggested the higher dose and increased exposure at 100 mg led to better anti-tumor effects. Although the MTD was not reached in the present study, dose groups 150 mg or higher were not expanded or explored further because of the apparent higher occurrence of AEs (Table 1). In the 150 mg group, the occurrence of drug-related grade 3 and higher AE, AE leading to drug discontinuation, dose interruption, and dose reduction all seemed to be more frequent than those in the 100 mg group. The drug exposure of D-0316 at 100 mg exceeded the efficacious exposure level of osimertinib at the approved dose of 80 mg. Considering the overall drug exposure and the risks and benefits of different doses, we suggest 100 mg as the RP2D, with an induction period at a lower dose to improve tolerance by patients in the first cycle of treatment and to ensure safety and efficacy during long-term treatment.

In summary, D-0316 is a third-generation irreversible TKI that is safe, tolerable, and apparently effective for patients who have locally advanced or metastatic NSCLC with EGFR T790M mutation and who previously received a first- or second-generation EGFR-TKI.

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Conflict of Interest
Lieming Ding: Betta Pharmaceuticals Co., Ltd. (E); Yang Wang: Betta Pharmaceuticals Co., Ltd. (E); Zhe Shi: InventisBio Co., Ltd. (E); Ling Zhang: InventisBio Co., Ltd. (E); Yaolin Wang: InventisBio Co., Ltd. (E); Shun Lu: AstraZeneca, Pfizer, Hutchison MediPharma, ZaiLab, GenomiCare, Yuhan Corporation,
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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

Figure 2. An illustration of intracranial tumor response in a patient with a measurable brain lesion (circled) that measured as 29 mm (longest diameter) during screening and reduced to 18 mm (38% reduction), achieving PR. The patient received D-0316 at 100 mg/day.
Figure 3. Changes in blood concentration of D-0316 after single-dose treatment (a) and cycle 1 day 15 treatment (b).
Table 1. Summary of adverse events (AEs) and the most common drug-related AEs by dose levels.

| All AEs                     | 25 mg (N = 1) | 50 mg (N = 34) | 75 mg (N = 4) | 100 mg (N = 42) | 150 mg (N = 3) | All (N = 84) |
|-----------------------------|---------------|----------------|---------------|-----------------|---------------|-------------|
| Any AE                      | 1 (100.0)     | 33 (97.1)      | 4 (100.0)     | 41 (97.6)       | 3 (100.0)     | 82 (97.6)   |
| Any drug-related AE         | 1 (100.0)     | 31 (91.2)      | 4 (100.0)     | 41 (97.6)       | 3 (100.0)     | 80 (95.2)   |
| Any AE grades 3-5           | 1 (100.0)     | 13 (38.2)      | 0             | 16 (38.1)       | 1 (33.3)      | 31 (36.9)   |
| Any drug-related AE grades 3-5 | 1 (100.0)   | 5 (14.7)       | 0             | 12 (28.6)       | 1 (33.3)      | 19 (22.6)   |
| AE leading to drug discontinuation | 0             | 4 (11.8)      | 0             | 9 (21.4)        | 1 (33.3)      | 14 (16.7)   |
| AE leading to dose interruption | 0             | 4 (11.8)      | 1 (25.0)      | 7 (16.7)        | 1 (33.3)      | 13 (15.5)   |
| AE leading to dose reduction | 0             | 0             | 1 (25.0)      | 2 (4.8)         | 1 (33.3)      | 4 (4.8)     |
| Serious AE                  | 1 (100.0)     | 8 (23.5)       | 0             | 11 (26.2)       | 0             | 20 (23.8)   |
| Serious drug-related AE     | 0             | 1 (2.9)        | 0             | 5 (11.9)        | 0             | 6 (7.1)     |

Most common (≥10%) drug-related AEs

**Platelet count decreased**
- Any grade: 0
- Grades 3-5: 0

**Electrocardiogram QT corrected interval prolonged**
- Any grade: 1 (100.0)
- Grades 3-5: 1 (100.0)

**Anemia**
- Any grade: 0
- Grades 3-5: 0

**Rash**
- Any grade: 1 (100.0)
- Grades 3-5: 0

**White blood cell decreases**
- Any grade: 0
- Grades 3-5: 0

**Hypertriglyceridemia**
- Any grade: 0
- Grades 3-5: 0

**Cholesterol high**
- Any grade: 0
- Grades 3-5: 0

**Headache**
- Any grade: 0
- Grades 3-5: 0

**Pruritus**
- Any grade: 0
- Grades 3-5: 0

**Cough**
- Any grade: 0
- Grades 3-5: 0

**AST elevation**
- Any grade: 0
- Grades 3-5: 0

**ALT elevation**
- Any grade: 0
- Grades 3-5: 0

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase.