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Clinical Trial Results

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.

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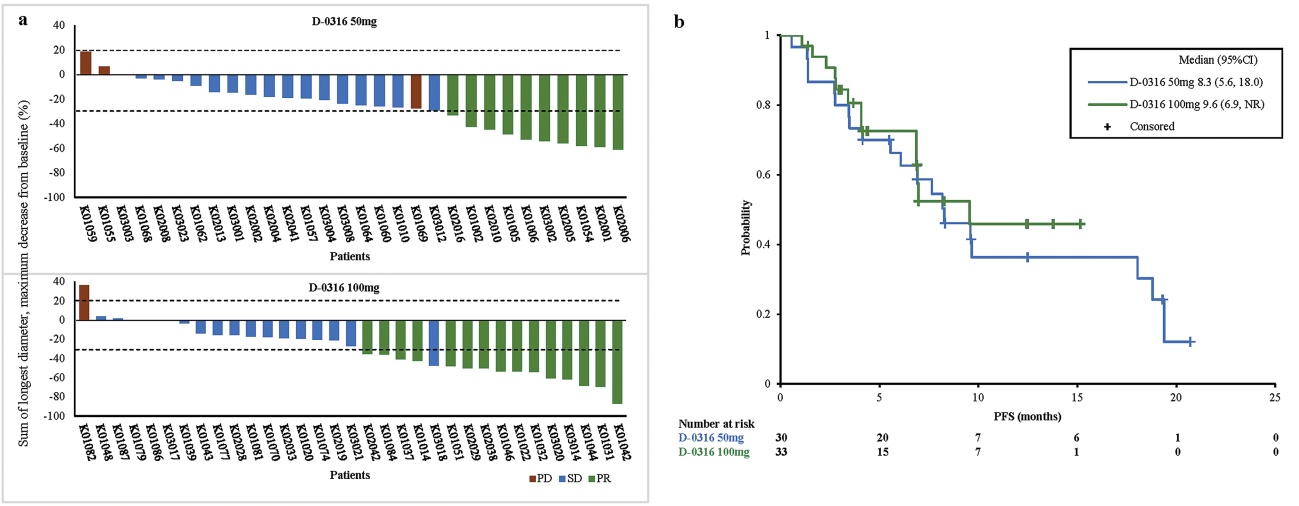

Figure 1. Efficacy results of D-0316. (a) Changes of tumor lesion size of patients in the 50 mg and 100 mg expansion groups (waterfall plot). (b) Kaplan–Meier curves of PFS in the 50 and 100 mg expansion groups.

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,[3,4] 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.

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.)
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.

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.)
Schedule of administration	Patients received D-0316 once daily under fasting conditions in each 21-day cycle.

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. 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	
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
Number of prior systemic therapies	Median (range): at least one prior EGFR TKI therapy
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	
Response assessment PR	*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 prolonged	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%	1%	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

Number evaluated for toxicity	Dose of drug: D-0316	Number with dose-limiting toxicity	Dose-limiting toxicity
1	25	0	
34	50	0	
4	75	0	
42	100	1	Grade 3 headache
3	150	0	

Pharmacokinetics/Pharmacodynamics: Total

Dose level	Dose of drug: D-0316, mg	Number enrolled	C_{max} (nmol/L), GeoMean	T_{max} (h) median	AUC_{0-24} (h × nmol/L), GeoMean	$T½$(h) mean	Accumulation ratio, Geomean
Single dose	25	1	79	4	1300	48	
Single dose	50	3	165	4	2750	47	
Single dose	75	4	177	6	2720	94	
Single dose	100	14	370	4	5600	77	
Single dose	150	3	346	4	5200	95	
Cycle 1 Day 15	25	1	292	4	5730		4.4
Cycle 1 Day 15	50	31	570	4	11 100		5.1
Cycle 1 Day 15	75	3	986	4	18 400		6.5
Cycle 1 Day 15	100	30	1230	4	23 400		4.5
Cycle 1 Day 15	150	3	1380	4	25 700		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,[3,4] 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.[5] 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.[6,7] 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.[8] 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.[9] 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.[5] 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.[10] 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%,[11] 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 T790Mmutated 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.

Acknowledgments

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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,

Menarini, InventisBio Co. Ltd., Roche (C/A), AstraZeneca, Roche, Hansoh, Hengrui Therapeutics (H), AstraZeneca, Hutchison, Bristol-Meyers Squibb, Heng Rui Beigene, Roche, Hansoh (RF). The other authors indicated no financial relationships.

(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

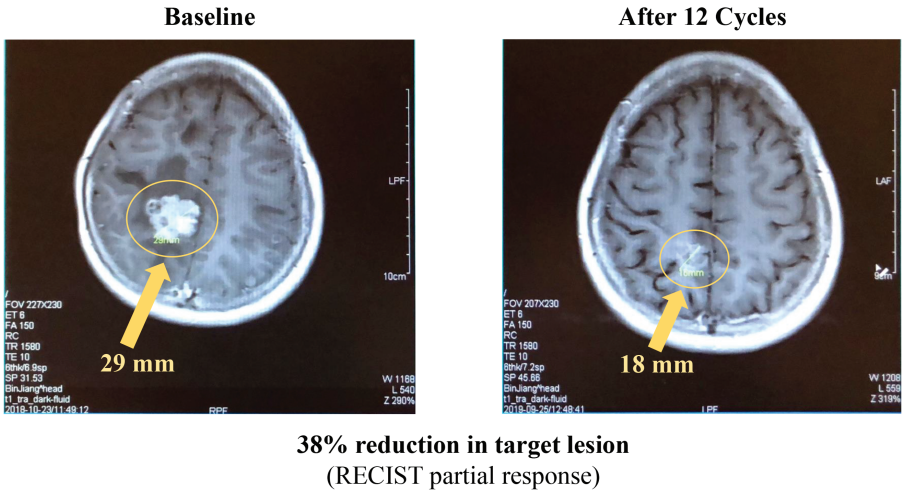

Figure 2. An illustration of intracranial tumor response in a patient with a measurable brain lesion (circled) that measured as 29 mm (longest diameter) during screening and reduced to 18 mm (38% reduction), achieving PR. The patient received D-0316 at 100 mg/day.

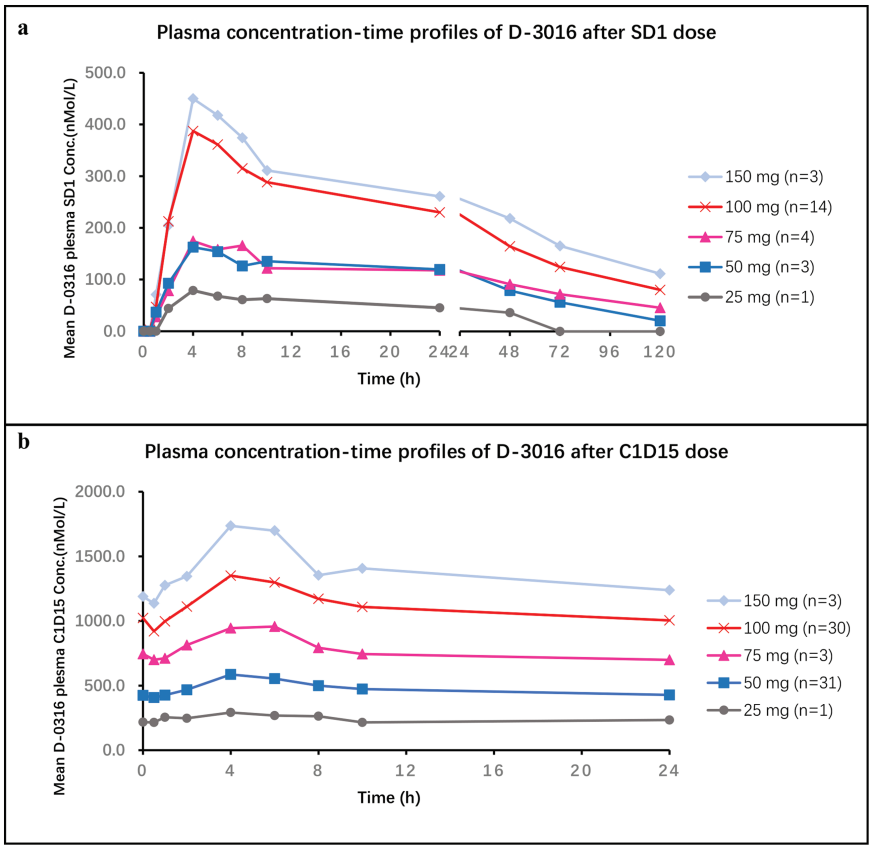

Figure 3. Changes in blood concentration of D-0316 after single-dose treatment (a) and cycle 1 day 15 treatment (b).

Table 1. Summary of adverse events (AEs) and the most common drug-related AEs by dose levels.

All AEs	25 mg	50 mg	75 mg	100 mg	150 mg	All
	(*N* = 1)	(*N* = 34)	(*N* = 4)	(*N* = 42)	(*N* = 3)	(*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	20 (58.8)	2 (50.0)	24 (57.1)	2 (66.7)	48 (57.1)
Grades 3-5	0	2 (5.9)	0	5 (11.9)	0	7 (8.3)
Electrocardiogram QT corrected interval prolonged						
Any grade	1 (100.0)	13 (38.2)	2 (50.0)	18 (42.9)	2 (66.7)	36 (42.9)
Grades 3-5	1 (100.0)	0	0	0	0	1 (1.2)
Anemia						
Any grade	0	9 (26.5)	1 (25.0)	16 (38.1)	1 (33.3)	27 (32.1)
Grades 3-5	0	1 (2.9)	0	0	0	1 (1.2)
Rash						
Any grade	1 (100.0)	11 (32.4)	0	15 (35.7)	0	27 (32.1)
Grades 3-5	0	0	0	0	0	0
White blood cell decreases						
Any grade	0	6 (17.6)	1 (25.0)	7 (16.7)	1 (33.3)	15 (17.9)
Grades 3-5	0	0	0	0	0	0
Hypertriglyceridemia						
Any grade	0	2 (5.9)	1 (25.0)	10 (23.8)	1 (33.3)	14 (16.7)
Grades 3-5	0	0	0	2 (4.8)	0	2 (2.4)
Cholesterol high						
Any grade	0	2 (5.9)	1 (25.0)	11 (26.2)	0	14 (16.7)
Grades 3-5	0	0	0	0	0	0
Headache						
Any grade	0	2 (5.9)	1 (25.0)	8 (19.0)	2 (66.7)	13 (15.5)
Grades 3-5	0	0	0	1 (2.4)	0	1 (1.2)
Pruritus						
Any grade	0	2 (5.9)	2 (50.0)	7 (16.7)	0	11 (13.1)
Grades 3-5	0	0	0	0	0	0
Cough						
Any grade	0	4 (11.8)	0	6 (14.3)	0	10 (11.9)
Grades 3-5	0	0	0	0	0	0
AST elevation						
Any grade	0	4 (11.8)	1 (25.0)	5 (11.9)	0	10 (11.9)
Grades 3-5	0	0	0	0	0	0
ALT elevation						
Any grade	0	2 (5.9)	1 (25.0)	6 (14.3)	0	9 (10.7)
Grades 3–5	0	0	0	0	0	0

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