A Phase I/IIa Study of DHP107, a Novel Oral Paclitaxel Formulation, in Patients with Advanced Solid Tumors or Gastric Cancer

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TRIAL INFORMATION

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• Sponsor: Daehwa Pharmaceutical Co. Ltd.
• Principal Investigator: Yoon-Koo Kang
• IRB Approved: Yes

LESSONS LEARNED

• Ideally, patients should have access to an oral formulation of paclitaxel, as well as an intravenous formulation, to allow development of regimens exploring alternate schedules and to avoid reactions to Cremophor EL (BASF Corp., Ludwigshafen, Germany, https://www.basf.com).
• DHP107 is a novel oral paclitaxel formulation that is a tolerable and feasible regimen for patients with gastric cancer, with data suggesting efficacy similar to that of intravenous paclitaxel.

ABSTRACT

Background. We evaluated the maximum tolerated dose (MTD) of DHP107, a novel oral paclitaxel formulation, and the efficacy and safety of the agent in patients with advanced solid tumors.

Patients and Methods. Phase I study: cohorts of 3–6 patients with advanced solid tumors received escalating DHP107 doses. Phase IIa study: patients with measurable advanced gastric cancer received DHP107, 200 mg/m² b.i.d., on days 1, 8, and 15 every 4 weeks. Pharmacokinetics, safety, and efficacy were analyzed.

Results. Phase I: 17 patients received a dose-escalating regimen of DHP107, 150–250 mg/m² b.i.d. Dose-limiting toxicities were neutropenia and febrile neutropenia. The MTD (recommended dose) for phase Ila was 200 mg/m² b.i.d. Phase Ila: 11 patients with measurable advanced gastric cancer in whom first-line therapy failed received DHP107 (MTD). Three confirmed partial responses were observed. Median progression-free survival of gastric cancer patients (n = 16) treated at the MTD was 2.97 (95% confidence interval, 1.67–5.40) months (Fig. 1). The most frequent grade 3/4 adverse events were neutropenia (35.3%) and leukopenia (17.6%) at the MTD (phase I and Ila combined; n = 17).

Conclusion. DHP107 showed good antitumor efficacy and was tolerable. The MTD (200 mg/m² b.i.d.) is recommended for use in further studies comparing DHP107 with standard intravenous paclitaxel therapy. The Oncologist 2017;22:129–e8

DISCUSSION

DHP107, developed by Daehwa Pharmaceutical Co. Ltd., is a lipid-based single-agent oral paclitaxel formulation that is systemically absorbed without the need for P-glycoprotein inhibitors or Cremophor EL (BASF Corp., Ludwigshafen, Germany, https://www.basf.com). We carried out a phase I/IIa study using a weekly regimen (days 1, 8, and 15) in which DHP107 was given b.i.d. to increase patients’ exposure to the drug to determine toxicities and the maximum tolerated dose. By using a b.i.d. regimen in this study, exposure at or above the therapeutic threshold (8.5 ng/mL) was maintained for approximately 24 hours.

In the phase I (dose-escalation) portion, 2 of 4 patients experienced dose-limiting toxicities (DLTs; febrile neutropenia) with DHP107, 225 mg/m² b.i.d.; 2 of 4 patients had DLTs (neutropenia and febrile neutropenia) with DHP107, 250 mg/m² b.i.d. No DLTs occurred among the 6 patients who received DHP107, 200 mg/m² b.i.d.; hence, this was considered the MTD. Overall, 200 mg/m² was tolerable in the day 1, 8, and 15 schedule, with neutropenia as the main side effect; only 77% of patients had grade 1 or 2 diarrhea and 35% had grade 1 or 2 nausea. In the phase Ila study, 11 patients with measurable advanced gastric cancer were enrolled at the MTD for a total of 17 patients who received DHP107, 200 mg/m² b.i.d., to allow preliminary evaluation of efficacy. On the basis of the optimal two-stage design, depending on patients’ responses, we...
planned to enroll up to 17 gastric cancer patients in the phase IIa study. When 11 patients had been recruited, 3 showed confirmed PRs, providing an overall response rate of 27.3% (95% confidence interval [CI], 0.0%–54.9%). As a result, additional enrollment was discontinued, and the efficacy was considered adequate to support further phase III study.

The development of an oral formulation of paclitaxel is an important goal for patient convenience and lessening side effects; it could allow the development of novel regimens, for low-dose, long exposure to paclitaxel. If oral paclitaxel is proven to deliver equally effective therapy, it could also replace intravenous paclitaxel in some regimens, thereby preventing infusion reactions due to Cremophor EL diluent. The current study indicates that DHP107 is active and safe enough for continued development.

Figure 1. Kaplan-Meier curve for progression-free survival in patients with gastric cancer in the efficacy-evaluable population (n = 16). These were patients with gastric cancer.

**Trial Information**

| Disease                     | Advanced cancer/solid tumor |
|-----------------------------|-----------------------------|
| Stage of disease/treatment  | Metastatic/advanced         |
| Prior Therapy               | No designated number of regimens |
| Type of study               | Phase I/IIa                 |
| Primary Endpoint            | Phase I: Maximum tolerated dose (MTD) |
|                             | Phase IIa: Response rate (RR) |
| Secondary Endpoint          | Safety                      |
| Secondary Endpoint          | Efficacy                    |
| Additional Details of Endpoints or Study Design | The aims of the current phase I/IIa study were to determine the MTD for repeated administration of DHP107 by weekly schedule in patients with metastatic solid tumors and to evaluate DHP107 efficacy in patients with advanced gastric cancer |
| Investigator’s Analysis     | Active and should be pursued further |

**Drug Information**

| Generic/Working name        | DHP107 (Oral paclitaxel) |
|-----------------------------|--------------------------|
| Company name                | Daehwa Pharmaceutical Co. Ltd. |
| Drug class                  | Tubulin/microtubules targeting agent |
| Dose                        | 200 mg/m² |
| Route                       | p.o. |
| Schedule of Administration  | DHP107 was administered b.i.d. on days 1, 8, and 15 of a 28-day cycle. The dose identified as the MTD was selected for the phase IIa portion of the study |
### Patient Characteristics (Phase I)

| Parameter                          | Value             |
|------------------------------------|-------------------|
| Number of patients, male           | 10                |
| Number of patients, female         | 7                 |
| Stage                              | IV                |
| Age                                | Median (range): 55 (30 – 67) |
| Number of prior systemic therapies | Median (range): not collected |
| Performance Status: ECOG           | 0 – 2             |
|                                    | 1 – 15            |
|                                    | 2 – 0             |
|                                    | 3 – 0             |
|                                    | unknown — 0       |
| Cancer Types or Histologic Subtypes| Gastric 13        |
|                                    | Colorectal 2      |
|                                    | Parotid gland 1   |
|                                    | Salivary gland 1  |

### Patient Characteristics (Phase IIa)

| Parameter                          | Value             |
|------------------------------------|-------------------|
| Number of patients, male           | 5                 |
| Number of patients, female         | 6                 |
| Age                                | 52 (33 – 70)      |
| Performance Status: ECOG           | 0 – 1             |
|                                    | 1 – 10            |
|                                    | 2 – 0             |
|                                    | 3 – 0             |
|                                    | unknown — 0       |
| Cancer Types or Histologic Subtypes| Gastric 11        |

### Primary Assessment Method

#### Test Arm: Total Patient Population (Phase I)

| Parameter                          | Value             |
|------------------------------------|-------------------|
| Number of patients enrolled        | 17                |
| Number of patients evaluable for toxicity | 17                  |
| Number of patients evaluated for efficacy | 17                  |

#### Test Arm: Total Patient Population (Phase IIa)

| Parameter                          | Value             |
|------------------------------------|-------------------|
| Number of patients enrolled        | 11                |
| Number of patients evaluable for toxicity | 11                  |
| Number of patients evaluated for efficacy | 11                  |
| Response assessment CR              | n = 0 (0%)        |
| Response assessment PR              | n = 3 (27.3%)     |
| Response assessment SD              | n = 3 (27.3%)     |
| Response assessment PD              | n = 5 (45.5%)     |
| (Median) duration assessments PFS   | 2.97 months       |
### Adverse Events

| Name                                      | All Cycles Grade | 1  | 2  | 3  | 4  | 5  | All Grades |
|-------------------------------------------|------------------|----|----|----|----|----|------------|
| Neutrophil count decreased                | *NC/NA*          | 12%| 0% | 35%| 29%| 24%| 0%         | 88%         |
| White blood cell decreased                |                  | 29%| 0% | 47%| 18%| 6% | 0%         | 71%         |
| Anemia                                    |                  | 94%| 0% | 0% | 6% | 0% | 0%         | 6%          |
| Febrile neutropenia                       |                  | 94%| 0% | 0% | 0% | 6% | 0%         | 6%          |
| Abdominal pain                            |                  | 41%| 53%| 6% | 0% | 0% | 0%         | 59%         |
| Alopecia                                  |                  | 6% | 65%| 29%| 0% | 0% | 0%         | 94%         |
| Anorexia                                  |                  | 53%| 41%| 6% | 0% | 0% | 0%         | 47%         |
| Diarrhea                                  |                  | 23%| 59%| 18%| 0% | 0% | 0%         | 77%         |
| Dyspepsia                                 |                  | 70%| 12%| 18%| 0% | 0% | 0%         | 30%         |
| Fatigue                                   |                  | 70%| 24%| 6% | 0% | 0% | 0%         | 30%         |
| Fever                                     |                  | 70%| 24%| 6% | 0% | 0% | 0%         | 30%         |
| Flu-like symptoms                         |                  | 88%| 6% | 6% | 0% | 0% | 0%         | 12%         |
| Myalgia                                   |                  | 53%| 41%| 6% | 0% | 0% | 0%         | 47%         |
| Nausea                                    |                  | 65%| 29%| 6% | 0% | 0% | 0%         | 35%         |
| Peripheral sensory neuropathy             |                  | 82%| 12%| 6% | 0% | 0% | 0%         | 18%         |
| Pruritus                                  |                  | 82%| 18%| 0% | 0% | 0% | 0%         | 18%         |
| Mucositis oral                            |                  | 82%| 6% | 0% | 12%| 0% | 0%         | 18%         |
| Vomiting                                  |                  | 59%| 41%| 0% | 0% | 0% | 0%         | 41%         |

*No change from baseline/no adverse event

Hematologic adverse events occurring in >5% of patients in all cycles and nonhematologic adverse events occurring in >10% of patients in all cycles at the 200 mg/m² dose level (n = 17).
Dose-Limiting Toxicities

| Dose Level | Dose of Drug: DHP107 | Number Enrolled | Number Evaluable for Toxicity | Number with a Dose-Limiting Toxicity | Dose-Limiting Toxicity Information |
|------------|----------------------|-----------------|------------------------------|--------------------------------------|-----------------------------------|
| 1          | 150 mg/m²            | 3               | 3                            | 0                                    | Grade 4 neutropenia over 5 days, Grade 3 febrile neutropenia |
| 2          | 200 mg/m²            | 3               | 3                            | 0                                    | Grade 3 febrile neutropenia |
| 3          | 250 mg/m²            | 4               | 4                            | 2                                    |                                  |
| 3A         | 225 mg/m²            | 4               | 4                            | 2                                    |                                  |
| 2          | 200 mg/m²            | 3               | 3                            | 0                                    |                                  |

Assessment, Analysis, and Discussion

Completion
Study completed

Investigator’s Assessment
Active and should be pursued further

Paclitaxel has proven efficacy in treating a variety of cancers and is widely used to treat ovarian, gastric, breast, and nonsmall cell lung cancers [1–4]. Because paclitaxel has poor solubility in water, pharmaceutical agents, such as Cremophor EL (BASF Corp., Ludwigshafen, Germany), are used as a vehicle to aid intravenous administration [5–8]. However, Cremophor EL can have biological implications, including hypersensitivity reactions [9]. Furthermore, it alters the pharmacokinetics of paclitaxel, causing it to have a nonlinear profile [10, 11].

A number of attempts have been made to reformulate paclitaxel to make it a more convenient and safer medication. Oral administration of paclitaxel is problematic because of low bioavailability related to P-glycoprotein (P-gp) and other membrane proteins in the gastrointestinal mucosa, which inhibit absorption. Moreover, cytochrome P450 isoenzymes in gastrointestinal tract and liver rapidly metabolize the drug [12, 13]. Development of an oral formulation has focused on improving the solubility and oral bioavailability of paclitaxel. To increase systemic exposure of oral paclitaxel, it has been coadministered with an orally applicable P-gp blocker, such as cyclosporine A [12, 13]. However, the oral formulation of a cytotoxic agent combined with a P-gp blocker has disadvantages because of potential interactions with concomitant medications, including substrates for P-gp and/or with cytochrome P450 3A [14].

DHP107, developed by Daehwa Pharmaceutical Co. Ltd., is a lipid-based single-agent oral paclitaxel formulation that is systemically absorbed without the need for P-gp inhibitors or Cremophor EL [15]. An animal study of DHP107 showed it has a similar antitumor effect compared with intravenous paclitaxel in human gastric cancer xenografts [16]. A previous phase I study in patients with advanced solid tumors refractory to all standard treatments showed no dose-limiting toxicities (DLTs) with a single dose of DHP107 ranging from 60 to 600 mg/m². DHP107 pharmacokinetics did not increase proportionally, and pharmacokinetic profiles, including area under the plasma concentration–time curve (AUC) and maximum plasma concentration (Cmax), plateaued at doses above 250 mg/m² [17].

Intravenous paclitaxel has been one of the most commonly used salvage chemotherapies in gastric cancer. Although there has been no phase III comparative study of weekly paclitaxel versus every-3-weeks paclitaxel in gastric cancer, a phase I study of weekly paclitaxel showed antitumor effects similar to historical data for a every-3-weeks regimen as salvage chemotherapy [18]. With frequent use of weekly intravenous paclitaxel in gastric cancer and with the lower AUC and Cmax of a single dose of DHP107 compared with every-3-weeks intravenous paclitaxel [17], a weekly schedule of DHP107 was adopted in the current study.

The aims of the current phase I/IIa study were to determine the maximum tolerated dose (MTD) for repeated administration of DHP107 by weekly schedule in patients with metastatic solid tumors and to evaluate DHP107 efficacy in patients with advanced gastric cancer. The results of this study will guide phase III studies to compare the safety and efficacy of DHP107 versus intravenous paclitaxel.

Therefore, we carried out this phase I/IIa study using a weekly regimen (days 1, 8, and 15) in which DHP107 was given as a divided dose on the treatment day to increase patients’ exposure to the drug to allow determination of DLTs and the MTD. In the phase I (dose-escalation) portion of our study, 2 of 4 patients experienced DLTs (febrile neutropenia) with DHP107, 225 mg/m² b.i.d., and 2 of 4 patients had DLTs (neutropenia and febrile neutropenia) with DHP107, 250 mg/m² b.i.d. No DLTs occurred among the 6 patients who received DHP107, 200 mg/m² b.i.d.; hence, this was determined as the MTD. After enrollment of additional patients, a total of 17 patients received DHP107, 200 mg/m² b.i.d. At this dose level, 1 patient experienced febrile neutropenia and only 3 experienced grade 3/4 neutropenia in whole cycles. As a result, the dose was deemed tolerable. The most frequent non-hematologic toxicities at the MTD were alopecia, diarrhea, and anorexia, which were generally of mild severity (grade 1/2). In the previously reported phase I study, 4 of 21 patients (19.0%) receiving a single administration of DHP107 at doses above 300 mg/m² experienced grade 3 diarrhea; the grade of diarrhea seemed to increase with dose [17]. It is likely that the lipid-based formulation of DHP107 leads to the increased incidence of diarrhea.

The pharmacokinetic parameters of DHP107, such as Cmax and AUCref, were not linear in the dose range of 150–250 mg/m² b.i.d. However, when the values of AUCref in the phase Ila study were standardized with administered dose and
ence of DHP107, 200 mg/m², in patients with advanced gastric cancer who received the 200 mg/m² b.i.d. dose. \(T_{\text{max}}\) values in the gastrectomy group were significantly lower (i.e., the drug was absorbed more rapidly) than in the nongastrectomy group; however, \(\text{AUC}_{\text{inf}}\) and \(C_{\text{max}}\) showed no significant difference by gastrectomy status. Therefore, the bioavailability of DHP107 is considered not to be affected by gastrectomy.

The efficacy results suggested that DHP107 is comparable to intravenous paclitaxel as a second-line treatment in patients with advanced gastric cancer. Generally, the objective of a phase IIa study is to establish whether an intervention has sufficient efficacy against the disease to ensure further research [21]. Although the population of this study was small, based on an optimal two-stage design, this regimen showed encouraging efficacy in poor-prognosis patients. The overall response rate was 27.3% in the 11 patients with measurable disease; median progression-free survival (PFS) was 2.97 months in the 16 patients with gastric cancer who received DHP107, 200 mg/m² b.i.d. These results are in line with previous studies of intravenous weekly paclitaxel, in which response rates of 16%–24% and median PFS of 2.1–2.6 months were reported [18, 22].

**REFERENCES**

1. Vergote I, Triep CG, Arnaud F et al. Neoadjuvant chemotherapy or primary surgery in stage II or IV ovarian cancer. N Engl J Med 2010;363:943–953.
2. Kang HJ, Chang HM, Kim TW et al. A phase II study of paclitaxel and capcetabine as a first-line combination chemotherapy for advanced gastric cancer. Br J Cancer 2009;98:316–322.
3. Di Leo A, Gomez HL, Aziz Z et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer [published correction appears in J Clin Oncol 2009;27:1923]. J Clin Oncol 2008;26:5544–5552.
4. Sandler A, Gray R, Perry MC et al. Paclitaxel-carboptalin alone or with bevacizumab for non-small-cell lung cancer [published correction appears in N Engl J Med 2007;356:318]. N Engl J Med 2006;355:2542–2550.
5. Sparreboom A, Van Asperen J, Mayer U et al. Limited oral bioavailability and active epithelial secretion of paclitaxel (Taxot) caused by p-glycoprotein in the intestine. Proc Natl Acad Sci USA 1997;94:2031–2035.
6. Rowinsky EK, Wright M, Monsarrat B et al. Clinical pharmacology and metabolism of Taxol (paclitaxel): Update 1993. Ann Oncol 1994;5(suppl 6):S7–S16.
7. Sonnichsen DS, Liu Q, Schuetz EG et al. Variability in human cytochrome P450 paclitaxel metabolism. J Pharmacol Exp Ther 1995;275:566–575.
8. Walle T, Walle K, Kumar GN et al. Taxol metabolism and disposition in cancer patients. Drug Metab Dispos 1995;23:506–512.
9. Weiss RB, Donehower RC, Wierink PH et al. Hypersensitivity reactions from taxol. J Clin Oncol 1990;8:1263–1268.
10. Kears M, Gianni L, Egorin MJ. Paclitaxel pharmacokinetics and pharmacodynamics. Semin Oncol 1995;3:16–23.
11. Gianni L, Kears CM, Giani A et al. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol 1995;13:180–190.
12. Maliné M, Beijnen JH, Rosing H et al. A phase I and pharmacokinetic study of bid daily dosing of oral paclitaxel in combination with cyclosporin A. Cancer Chemother Pharmacol 2001;47:347–354.
13. Maliné MM, Beijnen JH, Rosing H et al. Co-administration of GF120918 significantly increase the systemic exposure to oral paclitaxel in cancer patients. Br J Cancer 2001;84:42–47.
14. Binkhathlan Z, Lavasanifar A. p-glycoprotein inhibition as a therapeutic approach for overcoming...
multidrug resistance in cancer: Current status and future perspectives. Curr Cancer Drug Targets 2013; 13:326–346.

15. Hong JW, Lee IH, Kwak YH et al. Efficacy and tissue distribution of DHP107, an oral paclitaxel formulation. Mol Cancer Ther 2007;6:3239–3247.

16. Na YS, Jung KA, Yang SJ et al. Antitumor effects of oral paclitaxel DHP107 on gastric cancer xenografts. Cancer Res 2011;71(suppl 8):2539.

17. Hong YS, Kim KP, Lim HS et al. A phase I study of DHP107, a mucoadhesive lipid form of oral paclitaxel, in patients with advanced solid tumors: Cross-over comparisons with intravenous paclitaxel. Invest New Drugs 2013;31:616–622.

18. Hironaka Y, Zenda S, Boku N et al. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9: 16–18.

19. Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–247.

20. Jang Y, Jo YW, Lee H et al. Absorption profiles of an oral paclitaxel formulation, DHP107 with variable dosing intervals in mice. Abstract presented at the 40th Annual Meeting and Exposition of the Controlled Release Society; July 21–24, 2013; Hawaii Convention Center, Honolulu, Hawaii. Available at https://issuu.com/scisoc/docs/2013crsprogrambook. Accessed [DATE].

21. Simon R. Optimal two-stage designs for clinical trials. Control Clin Trials 1989;10:1–10.

22. Kodera Y, Ito S, Mochizuki Y et al. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric cancer (CCOG0302 Study). Anticancer Res 2007;27:2667–2671.

23. Liebmann JE, Cook JA, Lipschultz C et al. Cytotoxic studies of paclitaxel (Taxol) in human tumour cell lines. Br J Cancer 1993;68:1104–1109.

24. Raymond E, Hanususke A, Faiivre S et al. Effects of prolonged versus short-term exposure paclitaxel (Taxol) on human tumor colony-forming units. Anticancer Drugs 1997;8:379–385.

25. Jurado JM, Sanchez A, Pajares B et al. Combined oral cyclophosphamide and bevacizumab in heavily pre-treated ovarian cancer [published correction appears in Clin Transl Oncol 2008;10:772]. Clin Transl Oncol 2008;10:583–586.

26. Garcia AA, Hirte H, Fleming G et al. A trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 2008;26:76–82.

27. Pasquier E, Kavallaris M, Andre N. Metronomic chemotherapy: New rationale for new directions. Nat Rev Clin Oncol 2010;7:455–465.

**FIGURES AND TABLES**

**Figure 1.** Kaplan-Meier curve for progression-free survival in patients with gastric cancer in the efficacy-evaluable population (n = 16). These were patients with gastric cancer.

| Number at Risk | 16 | 15 | 14 | 13 | 12 | 11 | 9 | 8 | 7 | 6 | 5 | 4 | 3 | 2 | 1 |
|----------------|----|----|----|----|----|----|---|---|---|---|---|---|---|---|---|
| Number Censored | 0  | 0  | 0  | 0  | 0  | 0  | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Figure 2.** Plasma concentration of paclitaxel after oral administration of DHP107.
### Table 1. Baseline patient characteristics

| Characteristic                              | Phase I \((n = 17)\) | Phase IIa \((n = 11)\) |
|---------------------------------------------|------------------------|-------------------------|
| **Median age (range), yr**                  | 55 (30–67)             | 52 (33–70)              |
| **Sex**                                     |                        |                         |
| Male                                        | 10 (58.8)              | 5 (45.5)                |
| Female                                      | 7 (41.2)               | 6 (54.5)                |
| **ECOG performance status**                 |                        |                         |
| 0                                           | 2 (11.8)               | 1 (9.1)                 |
| 1                                           | 15 (88.2)              | 10 (90.9)               |
| 2                                           | 0 (0)                  | 0 (0)                   |
| **Site of primary tumor**                   |                        |                         |
| Stomach                                     | 13 (76.5)              | 11 (100)                |
| Colon or rectum                             | 2 (11.8)               | 0 (0)                   |
| Parotid gland                               | 1 (5.9)                | 0 (0)                   |
| Salivary gland                              | 1 (5.9)                | 0 (0)                   |
| **Disease location**a                       |                        |                         |
| Cardia                                      | 1 (7.7)                | 1 (9.1)                 |
| Body                                        | 3 (23.1)               | 4 (36.4)                |
| Antrum                                      | 8 (61.5)               | 5 (45.5)                |
| Diffuse                                     | 1 (7.7)                | 1 (9.1)                 |
| **Extent of disease**a                      |                        |                         |
| Metastatic                                  | 13 (100)               | 7 (63.6)                |
| Recurrent                                   | 0 (0)                  | 4 (36.4)                |
| Locally advanced                            | 0 (0)                  | 0 (0)                   |
| **Metastatic sites**                        |                        |                         |
| Lung                                        | 3 (17.6)               | 0 (0)                   |
| Lymph node                                  | 14 (82.4)              | 5 (45.5)                |
| Liver                                       | 9 (52.9)               | 3 (27.3)                |
| Bone                                        | 2 (11.8)               | 0 (0)                   |
| Others                                      | 4 (23.5)               | 7 (63.6)                |
| **Previous surgery**                        | 5 (29.4)               | 7 (63.6)                |

Unless otherwise noted, values are number (percentage) of patients.

*aIn total, 24 patients had gastric cancer (phase I, \(n = 13\); phase IIa, \(n = 11\)), which was classified by disease location and extent.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

### Table 2. Grade 3/4 adverse events in the first cycle of the phase I portion \((n = 17)\)

| Adverse events              | DHP107 dose level |
|-----------------------------|-------------------|
|                             | 150 mg/m² b.i.d. \((n = 3)\) | 200 mg/m² b.i.d. \((n = 6)\) | 225 mg/m² b.i.d. \((n = 4)\) | 250 mg/m² b.i.d. \((n = 4)\) |
|                             | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Total |
| Anemia                      | 2       | 0       | 0       | 0       | 0       | 0       | 1       | 1       | 1       | 1       | 4     |
| Neutropenia                 | 2       | 0       | 2       | 1       | 0       | 0       | 3       | 1       | 1       | 3       | 10    |
| Febrile neutropenia         | 0       | 0       | 0       | 0       | 2       | 0       | 1       | 0       | 3       | 0       | 3     |
| Hypoalbuminemia             | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 1       | 0       | 1     |
| Hypocalcemia                | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 1       | 0       | 1     |
| Hypokalemia                 | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 1       | 0       | 1     |
| Hypophosphatemia            | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 1       | 0       | 1     |
| Hypotension                 | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 1       | 0       | 1     |
| Leukopenia                  | 1       | 0       | 2       | 0       | 0       | 0       | 3       | 1       | 7       | 1       | 1     |
| Worsening anemia            | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 1       | 0       | 1     |

*aDose-limiting toxicity.*
Table 3. Antitumor efficacy in patients with measurable lesions in the phase Ila study (n = 11)

| Outcome             | Patients, n (%) | 95% CI |
|---------------------|-----------------|--------|
| Overall response rate | 3 (27.3)        | 0.0–54.9 |
| Complete response   | 0 (0)           | 0.0–0.0  |
| Partial response    | 3 (27.3)        | 0.0–54.9 |
| Stable disease      | 3 (27.3)        | 0.0–54.9 |
| Progressive disease | 5 (45.5)        | 14.6–76.3 |

Abbreviation: CI, confidence interval.

Table 4. Adverse events across all cycles in dose level 2 (200 mg/m²) group (n = 17)

| Adverse event                  | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--------------------------------|---------|---------|---------|---------|
| Hematologic toxicity           |         |         |         |         |
| Anemia                         | 0 (0.0) | 0 (0.0) | 1 (5.9) | 0 (0.0) |
| Febrile neutropenia            | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.9) |
| Leukopenia                     | 0 (0.0) | 8 (47.1)| 3 (17.6)| 1 (5.9) |
| Neutropenia                    | 0 (0.0) | 6 (35.3)| 5 (29.4)| 4 (23.5)|
| Nonhematologic toxicity        |         |         |         |         |
| Abdominal distension           | 0 (0.0) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Abdominal pain                 | 5 (29.4)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Abdominal pain, upper          | 4 (23.5)| 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Alopecia                       | 11 (64.7)| 5 (29.4)| 0 (0.0) | 0 (0.0) |
| Anorexia                       | 7 (41.2)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Burn                           | 0 (0.0) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Chill                          | 1 (5.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Cough                          | 1 (5.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Diarrhea                       | 10 (58.8)| 3 (17.6)| 0 (0.0) | 0 (0.0) |
| Dyspepsia                      | 2 (11.8)| 3 (17.6)| 0 (0.0) | 0 (0.0) |
| Edema limbs                    | 1 (5.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Fatigue                        | 4 (23.5)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Fever                          | 4 (23.5)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Flu-like symptoms              | 1 (5.9) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Hypertension                   | 0 (0.0) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Hyponatremia                   | 0 (0.0) | 0 (0.0) | 1 (5.9) | 0 (0.0) |
| Insomnia                       | 0 (0.0) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Myalgia                        | 7 (41.2)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Nausea                         | 5 (29.4)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Neurodermatitis                | 0 (0.0) | 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Obstruction gastric            | 0 (0.0) | 0 (0.0) | 1 (5.9) | 0 (0.0) |
| Peripheral sensory neuropathy  | 2 (11.8)| 1 (5.9) | 0 (0.0) | 0 (0.0) |
| Pruritus                       | 3 (17.6)| 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Stomatitis                     | 1 (5.9) | 0 (0.0) | 2 (11.8)| 0 (0.0) |
| Vomiting                       | 7 (41.2)| 0 (0.0) | 0 (0.0) | 0 (0.0) |

Values are expressed as number (percentage) of patients.
Table 5. Plasma pharmacokinetics of paclitaxel after oral administration of DHP107

| DHP107 dose (mg/m² b.i.d.) | Patients (n) | AUC_{inf} (ng·h/mL) | C_{max, 0–10h} (ng/mL) | CL/F (L/h/m²) | V_z/F (L/m²) |
|---------------------------|-------------|---------------------|------------------------|----------------|-------------|
| 150                       | 3           | 2,064.11 (541.85)   | 200.33 (52.52)         | 152.61 (42.01) | 2,778.37 (1,290.61) |
| 200                       | 17          | 2,180.44 (1,708.05) | 213.42 (108.49)        | 265.20 (135.40) | 5,112.16 (2,975.55) |
| 225                       | 3           | 5,088.09 (4,546.75) | 381.87 (300.32)        | 136.32 (80.39) | 2,318.43 (1,660.95) |
| 250                       | 4           | 4,830.53 (1,853.75) | 574.97 (468.68)        | 114.69 (40.59) | 2,249.34 (1,826.00) |

Unless otherwise noted, data are mean (standard deviation).
Abbreviations: AUC, area under the plasma concentration-time curve; CL/F, apparent total clearance of the drug from plasma after oral administration; C_{max}, maximum plasma concentration; V_z/F, apparent volume of distribution during terminal phase after non-intravenous administration.