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Clinical Cancer Research

# A Phase I Dose Escalation Study of Once-Weekly Oral Administration of Docetaxel as ModraDoc001 Capsule or ModraDoc006 Tablet in Combination with Ritonavir

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## Abstract

**Purpose:** Oral bioavailability of docetaxel is poor. Absorption could be improved by development of pharmaceutical formulations based on docetaxel solid dispersions, denoted ModraDoc001 capsule and ModraDoc006 tablet (both 10 mg) and coadministration of ritonavir, an inhibitor of CYP3A4 and P-glycoprotein. In this study, the safety, MTD, recommended phase II dose (RP2D), pharmacokinetics, and preliminary antitumor activity of oral docetaxel combined with ritonavir in a once-weekly continuous schedule was investigated.

**Patients and Methods:** Patients with metastatic solid tumors were included. Dose escalation was performed using a classical 3+3 design. Pharmacokinetic sampling was performed for up to 48 hours after drug administration. Safety was evaluated using CTCAE v3.0. Antitumor activity was assessed according to RECIST v1.0.

**Results:** Sixty-seven patients were treated at weekly docetaxel dosages ranging from 30 to 80 mg in combination with 100- or 200-mg ritonavir. Most common toxicities were nausea, vomiting, diarrhea and fatigue, mostly of grade 1–2 severity. No hypersensitivity reactions were observed. The area under the plasma concentration–time curve ($AUC_{0-48}$) of docetaxel at the RP2D of once-weekly 60-mg ModraDoc001 capsule with 100-mg ritonavir was 1,000 ± 687 ng/mL/hour and for once-weekly 60-mg ModraDoc006 tablet with 100-mg ritonavir, the $AUC_{0-48}$ was 1,790 ± 819 ng/mL/hour. Nine partial responses were reported as best response to treatment.

**Conclusions:** Oral administration of once-weekly docetaxel as ModraDoc001 capsule or ModraDoc006 tablet in combination with ritonavir is feasible. The RP2D for both formulations is 60-mg ModraDoc with 100-mg ritonavir. Antitumor activity is considered promising.

## Introduction

The anticancer agent docetaxel is registered for the treatment of breast, gastric, prostate, head and neck cancer, and non–small cell lung cancer (NSCLC) as an intravenous solution (1). The intravenous route of administration has limitations that might be overcome by oral administration. First, an indwelling intravenous catheter is needed for administrations and patients have to visit the hospital to receive docetaxel, whereas in case of an oral formulation administration would be more flexible and could potentially reduce costs of treatment, as patients do not need to be admitted to a day-care unit (2). A second advantage is that the solvents ethanol and polysorbate-80 are not needed in an oral formulation. Polysorbate-80 is considered to be at least partially the causative agent of the hypersensitivity reactions that occur during or shortly after administration of intravenous docetaxel (3, 4). Oral bioavailability of docetaxel is, however, low due to poor water solubility and high-first pass effect. The poor water solubility could be improved by the development of a solid dispersion formulation by freeze- or spray-drying of crystalline docetaxel in combination with a hydrophilic carrier and surfactant (5, 6). These solid dispersions consist of (more) amorphous docetaxel, and have a very small particle size and increased surface area, as compared with crystalline docetaxel. In combination with the hydrophilic carrier, this results in an increased apparent water solubility. Two solid dispersion formulations have been developed and tested in the clinic: the ModraDoc001 capsule (10-mg docetaxel, freeze-dried; ref. 5) and the ModraDoc006 tablet (10-mg docetaxel, spray-dried; ref. 6).The high first-pass effect of docetaxel is the result of metabolism in the intestinal lumen and the liver by the cytochrome p450 (CYP) enzyme CYP3A4 and active excretion from intestinal cells and via the bile into the gut lumen by drug transporters, such as P-glycoprotein (P-gp;

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## Translational Relevance

Although the active substance of ModraDoc (docetaxel) is by itself not a novel drug, the oral formulation, and the strategy of administration with a CYP3A4/Pgp inhibitor (i.e., ritonavir) as presented in this study represents a relevant proof-of concept with translation into potential benefits. The advantages of oral formulations of anticancer drugs in comparison with intravenous formulations are well-known and related to patient convenience, practicality, and reduced costs of treatment. Moreover, in the specific case of docetaxel, the lack of polysorbate 80 in the ModraDoc formulations appears to eliminate the occurrence of hypersensitivity reactions allowing treatment without dexamethasone premedication. The results obtained in phase I study presented in this article are considered promising and further development in phase II and III studies is currently pursued.

MDR1/ABCB1), multidrug resistance-associated protein 2 (MRP2,ABCC2), and organic anion-transporting polypeptides (OATP)1B1/1B3 (7–9). In both preclinical and clinical studies, the bioavailability of docetaxel was effectively increased by coadministration of inhibitors of either CYP3A4 or P-gp (10–12). Several candidates of so-called booster drugs have been investigated ultimately resulting in the selection of the CYP3A4 and P-gp inhibitor ritonavir (11, 13). Ritonavir has shown to be safe even at higher dosages than used in this study in the treatment of HIV, and it has been reported to be a safe and good booster of other protease inhibitors metabolized by CYP3A4, such as lopinavir (14, 15). In this phase I dose escalation study, two dose escalation arms of once-weekly dosing of oral docetaxel were investigated, exploring an oral drinking solution and subsequently ModraDoc001 capsule in combination with ritonavir (arm 1) and ModraDoc006 tablet in combination with 100-mg ritonavir (arm 2), respectively. The drinking solution was replaced by the capsule formulation after one dose level, because of its poor taste, poor stability, and limited dosing accuracy. The study was designed to establish safety, the MTD, and the recommended phase II dose (RP2D) of the ModraDoc001 capsule and ModraDoc006 tablet, respectively, when coadministered with ritonavir. Secondary aims included pharmacokinetics of docetaxel and preliminary antitumor activity.

## Patients and Methods

### Study design and treatment schedule

In this phase I, open-label, dose escalation study, three oral docetaxel formulations were investigated: an oral docetaxel drinking solution (Taxotere, Sanofi Aventis), ModraDoc001 10-mg capsule, and ModraDoc006 10-mg tablet. The study consisted of two dose escalation arms as shown Fig. 1. In the first arm, patients were treated in week 1 with once-weekly 20-mg intravenous docetaxel, as a 30-minute infusion (Taxotere, Sanofi Aventis). At the start of the intravenous docetaxel administration, patients took an oral dose of 100-mg ritonavir (Norvir Abbott) administered with 150 mL of tap water. The oral ritonavir dose was administered to allow for a calculation of the oral bioavailability of the oral formulations, which were always combined with 100-mg ritonavir. In week 2 and thereafter, patients received once-weekly 30-mg docetaxel as drinking solution (Taxotere) with 100-mg ritonavir at dose level 1. At the subsequent dose levels, patients received once-weekly oral ModraDoc001 capsules (5) combined with 100-mg ritonavir (ModraDoc001 capsule/100-mg ritonavir) in week 2 and beyond. Ritonavir was always administered orally simultaneously with oral docetaxel. After escalation to three additional dose levels, the ritonavir dose was increased from 100 mg to 200 mg and patients no longer received intravenous docetaxel in week 1.

After completion of the dose escalation with ModraDoc001 capsule/100-mg or 200-mg ritonavir, investigation of the ModraDoc006 tablet formulation (6) was performed in arm 2 of the study at two dose levels in combination with a fixed dose of 100-mg ritonavir, starting at the once-weekly 60-mg ModraDoc006 tablet/100-mg ritonavir dose, corresponding to the RP2D for the ModraDoc001 capsule/100-mg ritonavir. Ritonavir was always administered orally simultaneously with oral docetaxel.

Premedication consisted of granisetron 1 mg 1 hour prior to ModraDoc administration during cycle 1 and 2. Granisetron was thereafter administered as needed.

Patients were allowed to continue treatment with the oral drinking solution, ModraDoc001 capsule, or ModraDoc006 tablet in combination with ritonavir until disease progression or intolerable toxicity.

A classical 3+3 dose escalation design was used: three patients were enrolled at each dose level and the dose was escalated if no dose-limiting toxicity (DLT) occurred. If one DLT was observed in one of three patients, the dose was expanded to six patients. If either two of three or two of six patients experienced a DLT at a dose, this dose was deemed nontolerable. The previously tested lower dose was then expanded to six patients to assess the safety of this dose level. The MTD was defined as the dose at which DLTs occurred in fewer than two of six patients.

Dose escalation of docetaxel as a ModraDoc001 capsule or ModraDoc006 tablet was based on the safety evaluation and the pharmacokinetic data. Escalating levels were implemented considering also that only the 10-mg galenic formulation of ModraDoc001 capsule and ModraDoc006 tablet was available at the time the study was performed. All patients who received at least one dose of docetaxel in combination with ritonavir were considered evaluable for safety. All patients who completed the first 4 weeks of treatment where considered evaluable for DLT as well as patients with treatment interruption before week 4 due to adverse events (AEs) matching the DLT criteria. Patients not completing the first 4 weeks of treatment due to reasons not related to docetaxel (as drinking solution, ModraDoc001 capsule, or ModraDoc006 tablet) or ritonavir were replaced. The MTD was expanded to a maximum of 12 DLT-evaluable patients.

DLT was defined as any of the following events occurring in the first 4 weeks of treatment considered to be at least possibly, probably, or definitely related to docetaxel (as drinking solution, ModraDoc001 capsule, or ModraDoc006 tablet) or ritonavir: grade 3 or 4 nonhematologic toxicity (other than untreated nausea, vomiting, or diarrhea), grade 3 and 4 nausea, vomiting or diarrhea despite maximal support, grade 4 thrombocytopenia or grade 4 neutropenia for more than 7 consecutive days, grade 3 or 4 febrile neutropenia, and/or inability to begin the next course within 3 weeks of scheduled dosing due to toxicity.

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### Patient eligibility

Patients ≥ 18 years old with metastatic solid tumors were eligible. Other inclusion criteria were WHO performance status of ≤2, a life expectancy of at least 3 months, and adequate bone marrow, renal, and hepatic function. Patients taking concomitant treatment being strong P-gp and/or CYP3A4 inhibitors were excluded. Patients who had symptomatic cerebral or leptomeningeal metastases or pretreated with any anticancer treatment within four weeks prior to the first dose of oral docetaxel (as drinking solution, ModraDoc001 capsule, or ModraDoc006 tablet) were also excluded from the study (radiotherapy on a limited field for pain palliation was allowed). The study protocol was approved by the Medical Ethics Committee of the Netherlands Cancer Institute (Amsterdam, the Netherlands) and was conducted in accordance with the Declaration of Helsinki. All patients had to provide written informed consent prior to start of treatment. The study was registered under identifier ISCRTN32770468 (ISCRTN register).

### Study procedures

During the first 6 weeks of treatment, patients were seen weekly at the outpatient clinic for safety evaluation consisting of a physical examination, registration of adverse events according to the National Cancer Institute's Terminology Criteria for AE's version 3.0 (NCI-CTCAE v3.0; ref. 16) and their relation to study treatment, registration of concomitant medication, and laboratory assessments consisting of hematology and serum chemistry. After the first 6 weeks of treatment, patients were seen every 2 weeks. Tumor response evaluation was performed after 6 weeks and every 8 weeks thereafter in accordance with RECIST version 1.0 (17).

### Pharmacokinetics

Pharmacokinetic blood sampling was performed at predefined timepoints at day 1 and 8 or 15 of treatment. Samples for docetaxel pharmacokinetics were drawn from a peripheral intravenous catheter predose, postinfusion, and 0.25, 0.5, 1, 1.5, 2, 4, 7, 10, 24, and 48 hours after infusion of intravenous docetaxel. Pharmacokinetic sampling for docetaxel after oral administration of ModraDoc001 capsule/100-mg or 200-mg ritonavir was performed predose, 0.25, 0.75, 1, 1.5, 2, 4, 7, 10, 24, and 48 hours after dosing. Sampling for evaluation of ritonavir pharmacokinetic was performed predose, 0.5, 1, 2, 7, 10, and 24 hours after administration. pharmacokinetic sampling for docetaxel and ritonavir after administration of ModraDoc006 tablet/100-mg ritonavir was performed predose, 0.5, 1, 1.5, 2, 3, 4, 7, 10, 24, and 48 hours after administration. All samples were collected in lithium heparin tubes of 4 mL. Samples were centrifuged within 1 hour at 1,500 × *g* for 10 minutes at 4°C and stored at −20 °C until docetaxel and ritonavir quantification. Docetaxel was quantified in plasma by a high-performance liquid chromatography assay with tandem mass spectrometric detection (LC/MS-MS) as developed by Kuppens and colleagues (18) and later on by the LC/MS-MS method as described by Hendrikx and colleagues (19). All ritonavir samples were analyzed according to the method of Hendrikx and colleagues (19). Stable isotopically labeled docetaxel and ritonavir were used as internal standards. The lower limit of quantification of the assay was 0.5 ng/mL for docetaxel and 2.0 ng/mL for ritonavir. The assay was validated according to FDA guidelines (20) and the principles of Good Laboratory Practice (GLP).

### Statistical analysis

Individual noncompartmental pharmacokinetic parameters were determined using validated scripts in the R software package (version 3.01; ref. 21). The mean, SD, and coefficient of variation (CV) for the following pharmacokinetic parameters were calculated: maximum concentration ($C_{max}$), time to reach $C_{max}$ ($T_{max}$), the area under the plasma concentration–time curve between $t = 0$ and the last pharmacokinetic time point at 48 hours ($AUC_{0-48}$) and with extrapolation to infinity ($AUC_{0-inf}$), and terminal half-life ($t_{1/2}$).

The apparent bioavailability (F%) was calculated for patients who received during the first course 20 mg i.v. docetaxel in combination with ritonavir. This was done using Eq. (A).

$$F\% = \frac{AUC_{inf}\ (po)}{AUC_{inf}\ (iv)} \times \frac{Dose\ (iv)}{Dose\ (po)} \times 100\% \qquad \text{(A)}$$

## Results

### Patients

Overall, 67 patients were included in the study, of which five patients received docetaxel as the drinking solution, 43 patients as ModraDoc001 capsule, and 19 patients as ModraDoc006 tablet. Individual dose levels investigated and number of patients included per arm are presented in Fig. 1. One patient enrolled at the 80-mg ModraDoc006 tablet/100-mg ritonavir dose level did not start treatment due to clinical deterioration. Patients had a median age of 58 (range, 36–78) and 59 (range, 47–75) years in the ModraDoc001 capsule and ModraDoc006 tablet arm, respectively. Overall, the majority of patients were males (55%) and had a WHO PS ≤1 (93%). Patient demographics are presented in more detail in Table 1.

### Safety and tolerability

***Adverse events.*** The docetaxel drinking solution, ModraDoc001 capsule, and ModrDoc006 tablet (all combined with ritonavir) were well tolerated. Toxicity observed was mostly of grade 1 or 2 severity. Treatment-related toxicity (i.e., considered possibly, probably, or definitely related to study drug by the investigator) occurring in >5% of patients or grade ≥ 3 is presented in Table 2. The most commonly reported toxicities were diarrhea (70%), nausea (67%), fatigue (67%), and vomiting (42%).

***DLT.*** Seven patients experienced one or more DLTs during dose escalation of ModraDoc001 capsule/100- or 200-mg ritonavir. Reported DLTs were grade 4 neutropenia and dehydration (both observed in one patient), grade 3 diarrhea (6×), nausea (2×), vomiting (2×), fatigue (2×), elevated AST (2×), elevated ALT (2×), mucositis (1×), and anorexia (1×).

A total of three patients experienced DLTs during dose escalation of ModraDoc006 tablet/100-mg ritonavir. They were grade 3 diarrhea (1×), neutropenic fever (1×), and mucositis (1×). One patient had a DLT based on a delay of treatment for more than 3 weeks as a result of grade 2 treatment-related toxicities. DLT events are shown per patient and dose level in Table 3.

On the basis of the observed DLTs, the MTD for the ModraDoc001 capsule was once-weekly 60-mg ModraDoc001 capsule/200-mg ritonavir. The MTD was, however, not considered to be the RP2D, as at this dose level, several patients required dose modifications due to treatment-related toxicity, which was

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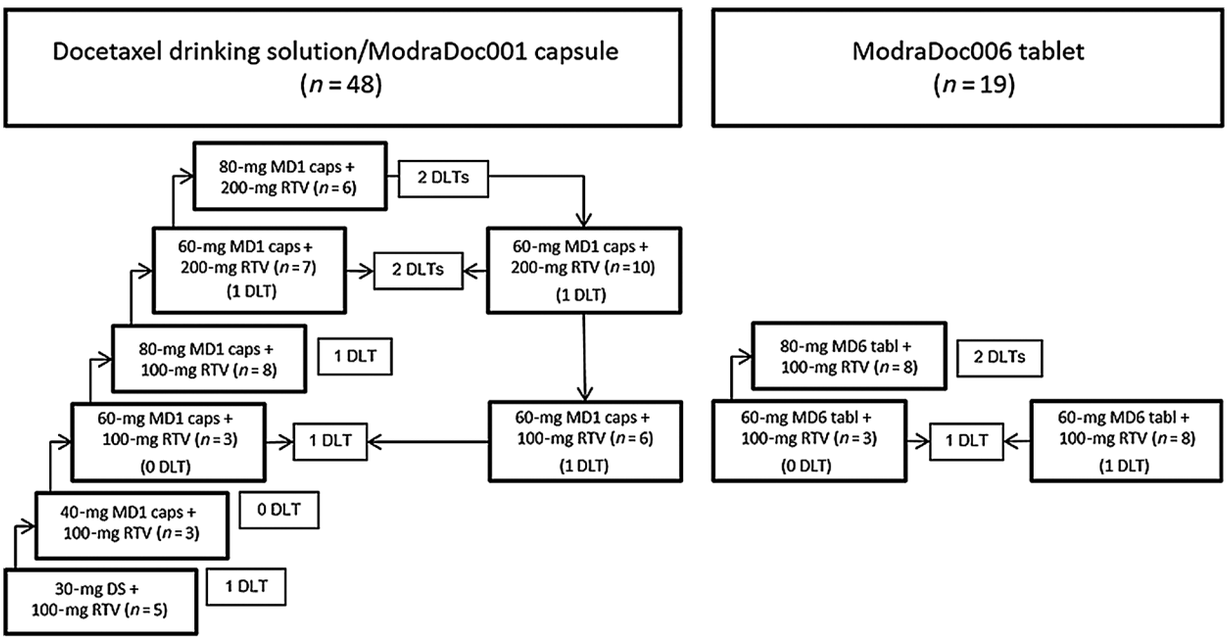


**Figure 1.**

Study schedule. Dose escalation performed with the capsule and tablet formulation. *N*, number of patients treated at a dose level. In the box, the number of DLTs observed at each dose level. Abbreviations: caps, capsule; MD1, ModraDoc001; MD6, ModraDoc006; *n*, number of patients; RTV, ritonavir; tabl, tablet.

**Table 1.** Baseline patient characteristics

| Formulation | Oral drinking solution or ModraDoc001 capsule | ModraDoc006 tablet |
|---|---|---|
| Number of patients | $n = 48$ | $n = 19$ |
| Gender | | |
| Male | 27 (56%) | 10 (53%) |
| Female | 21 (44%) | 9 (47%) |
| Age, | | |
| Median (range), y | 58 (36–78) | 59 (47–75) |
| WHO performance status | | |
| 0 | 21 (44%) | 12 (63%) |
| 1 | 22 (46%) | 7 (37%) |
| 2 | 5 (10%) | 0 |
| Primary tumor type | | |
| NSCLC | 22 (46%) | 8 (42%) |
| UCC | 5 (10%) | 0 |
| Ovarian | 3 (6%) | 1 (5%) |
| Unknown primary | 3 (6%) | 1 (5%) |
| Anal | 3 (6%) | 1 (5%) |
| Breast | 2 (4%) | 1 (5%) |
| Cholangiocarcinoma | 1 (2%) | 2 (11%) |
| Head and neck | 0 (0%) | 2 (11%) |
| Melanoma | 2 (4%) | 0 |
| Other | 8 (17%) | 3 (16%) |
| Prior therapy | | |
| Systemic therapy | 48 (100%) | 17 (89%) |
| Number of prior lines median (mean) | 2 (2) | 1 (2) |
| Range | 1–4 | 1–9 |
| Radiotherapy | 33 (69%) | 9 (47%) |
| Surgery | 26 (54%) | 9 (47%) |

Abbreviations: NSCLC, non–small cell lung cancer; UCC, urothelial cell carcinoma.

not dose-limiting. The related adverse events consisted essentially of long lasting grade $\leq 2$ fatigue, diarrhea, nausea, and anorexia leading to dose modifications after the DLT period (frequently shortly after the DLT period). The RP2D was determined as once-weekly 60-mg ModraDoc001 capsule/100-mg ritonavir.

On the basis of the DLTs and the overall toxicity observed, the MTD and RP2D for the ModraDoc006 tablet were determined as once-weekly 60-mg ModraDoc006 tablet/100-mg ritonavir.

***Serious adverse events/grade 3–4 toxicity.*** A total of 61 serious adverse events (SAEs) were reported in 22 (46%) patients treated with the oral drinking solution/100-mg ritonavir or ModraDoc001 capsule/100- or 200-mg ritonavir. A total of 23 SAEs (38%) occurring in 11 patients (23%) were considered related to study treatment: five events were of grade 2 severity and 18 events of grade $\geq 3$ severity. The most commonly observed treatment-related SAEs were diarrhea (occurring in six patients, 29%), nausea, and vomiting (both occurring in three patients, 14%). In patients treated with the oral drinking solution/100-mg ritonavir or ModraDoc001 capsule/100- or 200-mg ritonavir, 32 grade $\geq 3$ events were reported, of which 18 (56%) were considered to be SAEs. The most common grade $\geq 3$ events not considered to be SAE were fatigue in seven (50%) patients and neutropenia in two (14%) patients.

A total of 28 SAEs were reported in patients treated with ModraDoc006 tablet/100-mg ritonavir, of which eight (29%) were considered related to study treatment (four events were of

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**Table 2.** Adverse event reported as (possibly, probable, or definitely) related to oral docetaxel occurring in >7% of patients or grade ≥3, per dose level

| *n* = 66 patients | DS 30-mg RTV 100 mg | | MD1 40-mg RTV 100 mg | | MD1 60-mg RTV 100 mg | | MD1 80-mg RTV 100 mg | | MD1 60-mg RTV 200 mg | | | MD1 80-mg RTV 200 mg | | | MD6 60-mg RTV 100 mg | | | MD6 80-mg RTV 100 mg | | N event |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Adverse event** | **Gr1–2** | **Gr3** | **Gr1–2** | **Gr3** | **Gr1–2** | **Gr3** | **Gr1–2** | **Gr3** | **Gr1–2** | **Gr3** | **Gr4** | **Gr1–2** | **Gr3** | **Gr4** | **Gr1–2** | **Gr3** | **Gr5** | **Gr1–2** | **Gr3** | **(% event)** |
| Diarrhea | 1 | 1 | 0 | 0 | 3 | 0 | 9 | 2 | 9 | 2 | 0 | 3 | 2 | 0 | 8 | 1 | 0 | 5 | 0 | 46 (70%) |
| Nausea | 2 | 0 | 1 | 0 | 2 | 0 | 10 | 2 | 11 | 0 | 0 | 5 | 0 | 0 | 7 | 0 | 0 | 4 | 0 | 44 (67%) |
| Fatigue/malaise | 3 | 0 | 1 | 0 | 1 | 1 | 9 | 2 | 9 | 2 | 0 | 2 | 2 | 0 | 7 | 0 | 0 | 5 | 0 | 44 (67%) |
| Vomiting | 1 | 0 | 0 | 0 | 1 | 0 | 6 | 2 | 4 | 0 | 0 | 3 | 0 | 0 | 8 | 0 | 0 | 3 | 0 | 28 (42%) |
| Alopecia | 1 | 0 | 0 | 0 | 1 | 0 | 5 | 0 | 7 | 0 | 0 | 2 | 0 | 0 | 4 | 0 | 0 | 2 | 0 | 22 (33%) |
| Mucositis | 1 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 5 | 0 | 0 | 2 | 1 | 0 | 2 | 0 | 0 | 1 | 1 | 16 (24%) |
| Constipation | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 3 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 9 (13%) |
| Weight loss | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 0 | 9 (13%) |
| Abdominal pain | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 3 | 0 | 8 (12%) |
| Dysgeusia | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 2 | 0 | 8 (12%) |
| Nail changes | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 (10%) |
| Anorexia | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 | 7 (10%) |
| Sensory neuropathy | 0 | 0 | 0 | 0 | 1 | 0 | 2 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 (10%) |
| Neutropenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 6 (9%) |
| Abdominal cramps | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 | 1 | 0 | 6 (9%) |
| AST increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 (4%) |
| Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 3 (4%) |
| Leukocytopenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 3 (4%) |
| ALT increased | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (3%) |
| Thrombocytopenia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (3%) |
| Respiratory insufficiency | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 (1%) |
| Dehydration | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 (1%) |
| Gastritis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1%) |
| Duodenal ulcer | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1%) |
| Neutropenic fever | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 (1%) |

Abbreviations: caps, capsule; DS, docetaxel drinking solution; gr, grade; *n*, number of patients; MD1, ModraDoc001; MD6, ModraDoc006; RTV, ritonavir; tabl, tablet.

grade 2 and four events of grade ≥ 3 severity). Treatment-related SAEs occurred in four (22%) patients and consisted of mucositis (2×, 25%), diarrhea (1×, 13%), fatigue (1×, 13%), nausea (1×, 13%), neutropenic fever (1×, 13%), and respiratory failure (1×, 13%). The last SAE resulted in a death possibly related to study drug (reported as a separate SAE) occurring in a 64-year-old female patient with an esophageal carcinoma. After 11 weeks of treatment with ModraDoc006 tablet/ritonavir, the patient was admitted with respiratory failure, which could not clearly be attributed to underlying disease or to an infectious origin. As a relation with study drug (e.g., docetaxel-induced pneumonitis) could not be ruled out, the event was considered to be possibly related to ModraDoc006/ritonavir. Overall, eight adverse events of grade ≥ 3 severity were observed, of which four (50%) were considered SAEs. The grade ≥ 3 events not considered to be SAEs were dyspnea, diarrhea, neutropenia, and leukocytopenia (all occurred once and in patients who also experienced a DLT or SAE).

**Table 3.** DLTs observed in the dose escalation with the ModraDoc001 capsule and ModraDoc006 tablet

| Dose level | DLT (CTCAE v3.0) |
|---|---|
| ModraDoc001 capsule dose escalation | |
| 30-mg DS/100-mg RTV | Grade 3 diarrhea |
| 60-mg MD1/100-mg RTV | Grade 3 vomiting and nausea |
| 80-mg MD1/100-mg RTV | Grade 3 diarrhea, vomiting and nausea |
| 60-mg MD1/200-mg RTV | Grade 3 diarrhea, elevated AST and ALT |
| | Grade 3 diarrhea, fatigue and elevated AST and ALT |
| 80-mg MD1/200-mg RTV | Grade 4 dehydration, grade 3 diarrhea and mucositis |
| | Grade 4 neutropenia, grade 3 diarrhea, fatigue and anorexia |
| ModraDoc006 tablet dose escalation | |
| 60-mg MD6/100-mg RTV | Grade 3 diarrhea |
| 80-mg MD6/100-mg RTV | Grade 3 neutropenic fever, mucositis |
| | Delay of >3 weeks due to grade 2 toxicities |

Abbreviations: DS, docetaxel drinking solution; MD1, ModraDoc001; MD6, ModraDoc006; RTV, ritonavir.

***Pharmacokinetics.*** Pharmacokinetic parameters of docetaxel are presented in Table 4 for intravenous docetaxel, the oral docetaxel drinking solution, the ModraDoc001 capsule, and the ModraDoc006 tablet formulation, respectively. In Fig. 2, the plasma concentration–time curves of docetaxel per dose level are presented for in the ModraDoc001 capsule/100-mg ritonavir (Fig. 2A), in ModraDoc001 capsule/200-mg ritonavir (Fig. 2B), and in the ModraDoc006 tablet/100-mg ritonavir (Fig. 2C).

The mean $AUC_{0-48}$ ± SD and $C_{max}$ ± SD after intravenous administration of 20-mg docetaxel/100-mg oral ritonavir were 537 ± 255 ng/mL/hour and 478 ± 208 ng/mL, respectively. The mean $AUC_{0-48}$ ± SD and $C_{max}$ ± SD after administration of 30-mg docetaxel drinking solution/100-mg ritonavir were 488 ± 250 ng/mL/hour and 161 ± 183 ng/mL, respectively. The mean $AUC_{0-48}$ and $C_{max}$ of docetaxel increased with dose for the ModraDoc001 capsule. $C_{max}$ of docetaxel did not increase with the increase of ritonavir from a 100-mg to a 200-mg dose, while an increase in the docetaxel $AUC_{0-48}$ was observed with the increase in ritonavir dose. The mean $AUC_{0-48}$ ± SD at the RP2D of 60-mg ModraDoc001/100-mg ritonavir and at the

**Table 4.** Pharmacokinetic parameters of once-daily dosing of docetaxel as an oral drinking solution (DS), ModraDoc capsule, or tablet combined with either 100-mg or 200-mg ritonavir[a]

| | Docetaxel i.v., 20-mg oral ritonavir 100 mg ($n = 19$) | Docetaxel DS, 30-mg ritonavir 100 mg ($n = 5$) | ModraDoc001 Caps, 40-mg ritonavir 100 mg ($n = 3$) | ModraDoc001 Caps, 60-mg ritonavir 100 mg ($n = 9$) | ModraDoc001 Caps, 80-mg ritonavir 100 mg ($n = 8$) | ModraDoc001 Caps, 60-mg ritonavir 200 mg ($n = 17$) | ModraDoc001 Caps, 80-mg ritonavir 200 mg ($n = 6$) | ModraDoc006 Tabl, 60-mg ritonavir 100 mg ($n = 11$) | ModraDoc006 Tabl, 80-mg ritonavir 100 mg ($n = 7$) |
|---|---|---|---|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) mean ± SD | 478 ± 208 (43%) | 161 ± 183 (113%) | 63.4 ± 50.0 (79%) | 177 ± 136 (77%) | 264 ± 122 (46%) | 170 ± 106 (62%) | 226 ± 56.1 (25%) | 229 ± 241 (105%) | 178 ± 163 (91%) |
| (CV%) geo-mean (90% CI) | 438 (361–532) | 102 (40.1–258) | 50.5 (19.4–131) | 127 (67.3–241) | 240 (172–335) | 145 (109–192) | 220 (176–274) | 162 (97.6–268) | 134 (73.9–242) |
| $AUC_{0-48}$ (ng/mL/h) mean ± SD | 537 ± 255 (48%) | 488 ± 250[b] (51%) | 306 ± 150 (49%) | 1,000 ± 687 (69%) | 1,483 ± 687 (52%) | 1,631 ± 1268 (78%) | 1,790 ± 819 (46%) | 1,493 ± 1,449 (97%) | 1471 ± 935 (64%) |
| (CV%) geo-mean (90% CI) | 487 (398–596) | 572 (234–1,400) | 276 (143–535) | 793 (478–1,315) | 1,345 (982–1841) | 1,287 (921–1,570) | 1,656 (1,182–2,320) | 1,108 (698–1,759) | 1179 (663–2096) |
| $AUC_{0-inf}$ (ng/mL/h) mean ± SD (CV%) | 598 ± 281 (47%) | 476 ± 308[c] (65%) | 337 ± 146 (43%) | 1,097 ± 764 (70%) | 1,581 ± 795 (50%) | 1,308 ± 710[d] (52%) | 2,014 ± 1,630 (80%) | 1,709 ± 1,678[e] (97%) | 1598 ± 1279[f] (80%) |
| geo-mean (90% CI) | 542 (442–663) | 651 (248–1,710) | 313 (177–552) | 868 (523–1,440) | 1,444 (1,068–1,952) | 1,128 (809–1,574) | 1,858 (1,318–2,619) | 1,224 (754–2,064) | 1297 (508–2654) |
| $T_{max}$ (h) Mean ± SD (CV%) | EOI | 1.35 ± 0.469 (35%) | 1.32 ± 0.40 (31%) | 2.45 ± 0.985 (40%) | 2.19 ± 0.752 (34%) | 4.03 ± 2.45 (61%) | 2.37 ± 0.792 (33%) | 3.37 ± 1.50 (44%) | 4.59 ± 1.71 (37%) |
| geo-mean 90% CI of GM | | 1.28 (0.92–1.77) | 1.27 (0.86–1.88) | 2.29 (1.79–2.92) | 2.11 (1.74–2.56) | 3.41 (2.57–4.53) | 2.29 (1.84–2.85) | 3.11 (2.44–3.96) | 4.35 3.35–5.64 |
| $t_{1/2}$ (h) Mean ± SD (CV%) | 17.6 ± 3.91 (22%) | 16.6 ± 3.89[c] (23%) | 18.1 ± 5.93 (33%) | 16.4 ± 1.53 (9.3%) | 13.9 ± 3.96 (28%) | 16.5 ± 4.17[d] (25%) | 17.6 ± 3.64 (21%) | 17.4 ± 3.56[e] (20%) | 17.5 ± 3.08[f] (18%) |
| geo-mean (90% CI) | 17.2 (15.5–19.0) | 11.1 (6.34–19.4) | 17.5 (12.2–25.1) | 16.4 (15.4–17.4) | 13.3 (10.4–17.0) | 16.1 (14.0–18.4) | 17.3 (14.6–20.5) | 16.5 (14.9–19,6) | 15.4 (14.8–20.2) |

Abbreviations: caps, capsule; 90% CI, 90% confidence interval of the geometric mean; $C_{max}$, maximum concentration measured; CV%, coefficient of variation, DS, drinking solution; EOI, end of infusion; geo-mean, geometric mean; tabl, tablet; $T_{max}$, time at which $C_{max}$ was measured; $t_{1/2}$, terminal half-life.

[a]Results are shown for the first dose of oral docetaxel.

[b]$n = 4$ (incomplete pharmacokinetics of one patient).

[c]$n = 3$.

[d]$n = 12$.

[e]$n = 10$.

[f]$n = 5$ (unreliable regression).

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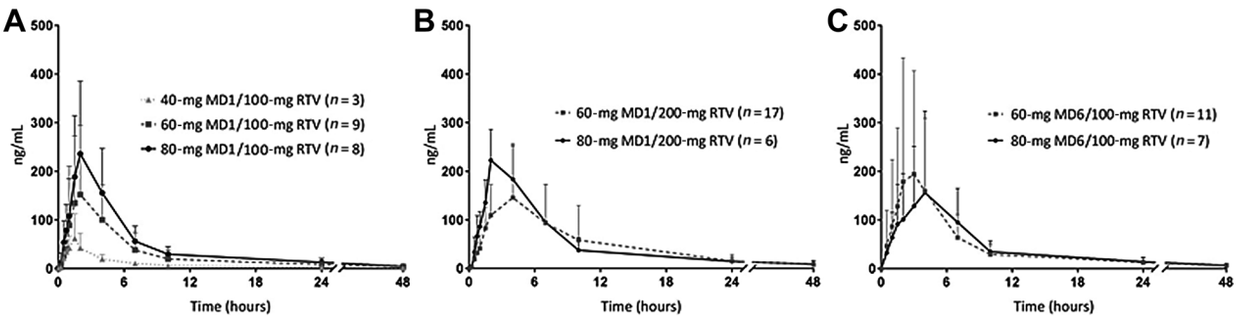


**Figure 2.**

Plasma concentration–time curves of docetaxel. Plasma concentration–time curves of docetaxel in the ModraDoc capsule (MD1)/100-mg ritonavir (cycle 2) in combination with either 100-mg (RTV; **A**), in the ModraDoc capsule/100-mg ritonavir (MD1; cycle 1; **B**), and in the ModraDoc tablet (MD6)/100-mg ritonavir (cycle 1; **C**). Abbreviations: *n*, number of patients; MD1, ModraDoc001; MD6, ModraDoc006; RTV, ritonavir.

MTD of 60-mg ModraDoc001/200-mg ritonavir were 1,000 ± 687 ng/mL/hour and 1,631 ± 1,268 ng/mL/hour, respectively. The mean $C_{max}$ ± SD at the RP2D and at the MTD for ModraDoc001 was 177 ± 136 ng/mL and 170 ± 106 ng/mL, respectively.

Mean $AUC_{0-48}$ and $C_{max}$ reached at the MTD/RP2D of 60-mg ModraDoc006 tablet/100-mg ritonavir were 1,492 ± 1,449 ng/mL/hour and 229 ± 241 ng/mL, respectively. The relatively high $AUC_{0-48}$ and $C_{max}$ observed at the MTD were driven by the results obtained in one patient, reporting an $AUC_{0-48}$ that was 5.2-fold higher (5,590 ng/mL/hour) and $C_{max}$ that was 5.7-fold higher (914 ng/mL) as compared with the other patients treated with the same dose. This was the same patient who experienced a death event possibly related to docetaxel treatment.

$T_{max}$ was 1 hour later for the ModraDoc006 tablet, compared with the $T_{max}$ of the ModraDoc001 capsule, independently of the docetaxel dose (3.47 ± 1.6 hours and 2.29 ± 0.93 hours, respectively). Mean $t_{1/2}$ was comparable for the ModraDoc001 capsule and the ModraDoc006 tablet: $t_{1/2}$ was 16.4 ± 3.7 hours and 17.5 ± 3.3 hours, respectively, independently of the docetaxel dose administered.

The estimated bioavailability of the drinking solution was 85% (SD ± 59%) and of the ModraDoc001 capsule/100-mg ritonavir, it was 65% (SD ± 22%). In Table 5, the dose-adjusted ratio of the geometric mean and its 90% confidence interval of intravenous docetaxel versus either the ModraDoc001 capsule/100-mg ritonavir or ModraDoc006/100-mg ritonavir at the respective RP2D are shown.

***Antitumor activity.*** A total of 41 of the 48 patients treated with the oral drinking solution or ModraDoc001 capsule (combined with 100-mg or 200-mg ritonavir) were evaluable for efficacy. A total of six patients (15%) reported a partial response, of which three were confirmed after a minimum of 4 weeks. No complete responses were observed. A total of 23 patients had stable disease as best response to treatment. Median time on study in patients experiencing clinical benefit was 19 (range, 3–72) weeks.

A total of 14 of the 19 patients treated with ModraDoc006 tablet/100-mg ritonavir were evaluable for efficacy. Three patients (21%) experienced a partial response, of which one was confirmed after a minimum of 4 weeks. No complete responses were observed. Seven patients had stable disease as best response to treatment. Median time on study in patients experiencing clinical benefit was 13 (range, 6–28) weeks.

**Table 5.** Comparison between pharmacokinetics of the intravenous docetaxel and the ModraDoc001 and ModraDoc006 formulations, respectively, by calculation of the dose-adjusted geometric mean (90% CI)

| | IV versus ModraDoc001 | IV versus ModraDoc006 |
|---|---|---|
| $C_{max}$ | | |
| Ratio of geo-mean (90% CI) | 11.4 (5.57–19.2) | 8.96 (4.99–13.3) |
| $AUC_{0-48}$ | | |
| Ratio of geo-mean (90% CI) | 1.84 (1.12–3.04) | 1.32 (0.84–2.07) |
| $AUC_{0-inf}$ | | |
| Ratio of geo-mean (90% CI) | 1.87 (1.13–3.09) | 1.33 (0.85–2.08) |

## Discussion

We previously published the results of a dose escalation study of twice-daily once-weekly oral docetaxel either as ModraDoc001 or ModraDoc006 combined with ritonavir (22). In the current dose-finding study, the continuous once-weekly administration of oral docetaxel as ModraDoc001 capsule or ModraDoc006 tablet coadministered with ritonavir was explored. On the basis of the observed DLTs, the MTD was established as once-weekly 60-mg ModraDoc001 capsule/200-mg ritonavir and once-weekly 60-mg ModraDoc006 tablet/100-mg ritonavir.

Treatment-related toxicity was mostly of grade 1 and 2 severity and was manageable with dose modifications and interruptions. The most commonly reported treatment-related adverse events consisted of nonhematologic toxicities.

Of note, hypersensitivity reactions and fluid retention (well-known adverse events reported for the docetaxel intravenous formulation) were not observed despite the lack of premedication with corticosteroids. This is probably due to the fact that oral ModraDoc001 capsule and ModraDoc006 tablet formulations lack the excipient polysorbate-80 (3, 4). Furthermore, no grade 3 peripheral neuropathy or other neurotoxicity was observed, while this is reported in about 3% of patients after weekly intravenous docetaxel (23). Partial (13 patients, 19%) or complete hair loss (nine patients, 13%; alopecia) was reported in 22 patients, whereas for weekly intravenous docetaxel partial and complete hair loss are observed in 12.5% and 58.3% of patients, respectively (24). The incidence of severe neutropenia and neutropenic fever was limited [six patients (9%) and one patient (1.5%),

respectively] and was dose-limiting in only one patient. These findings are in line with a meta-analysis published by di Miao and colleagues showing a reduction in bone marrow suppression (in particular neutropenia) and a slight increase in nonhematologic toxicity when a weekly intravenous docetaxel schedule was compared with a 3-weekly administration (25). The occurrence of grade 3 diarrhea in our study was relatively high with the oral formulations (11% of patients). This was not unexpected in view of the oral route of administration with expected local toxicity and the relevant preclinical studies reported in the literature over this issue (26), and indeed treatment recommendations for the management of diarrhea with loperamide were included in the study protocol. Loperamide was administered according to standard practice, starting after the first occurrence of diarrhea and escalating up to a maximum dose of 16 mg a day, when necessary. Diarrhea was observed at higher frequency and severity at the highest dose levels. At lower dose levels (including the MTD/RP2D), diarrhea was manageable with loperamide and/or dose modifications. Of note, grade 3 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevations as expression of hepatic toxicity were observed in three (4%) and two (3%) patients, respectively, and only when other DLTs were observed. All the AST/ALT elevations promptly recovered to grade $\leq 1$ after dose interruption.

The exposure to docetaxel in terms of $AUC_{0-inf}$ at the RP2D for both the ModraDoc001 capsule and the ModraDoc006 tablet formulations was in a concentration range comparable with continuous weekly intravenous docetaxel dosed at 30–36 mg/m$^2$ (27–29) given according to either a continuous or an intermittent weekly schema (i.e., day 1, 8, 15 every 28 days). However, the interpatient variability in terms of $AUC_{0-inf}$ observed after administration of the oral formulations was relatively high, with CV% ranging from 49% to 97%, compared with CV% ranges of 23%–30% reported in the literature (29, 30). To try to reduce the observed variability, a subsequent clinical study investigating a twice-daily once-weekly administration of oral docetaxel as either ModraDoc001 or ModraDoc006 combined with ritonavir was initiated (22). In our study, an increase in the dose of the boosting drug ritonavir from 100 mg to 200 mg was able to increase the exposure to docetaxel. Ritonavir significantly boosted the AUC of oral docetaxel as oral docetaxel without booster reaches low and negligible systemic exposure (10, 12).

Antitumor activity of ModraDoc001 capsule/100-mg or 200-mg ritonavir and ModraDoc006 tablet/with 100-mg ritonavir was reported in known docetaxel-sensitive tumors: partial responses were observed in three patients with NSCLC, in two patients with an unknown primary tumor and in one patient with ovarian, head and neck, anal and esophageal carcinoma, respectively. This preliminary activity is considered promising, in view also of the heavily pretreated patient population enrolled with some of the patients having received up to nine lines of systemic chemotherapy. The majority of tumor responses was observed at higher dose levels, suggesting a linear dose–response relationship. However, the number of patients experiencing tumor response was too low to allow any conclusion on this issue. Of note, previous treatment with a taxane was received by seven patients (two patients were pretreated with docetaxel and five patients with paclitaxel). Partial remission (one patient) and stable disease (two patients) were reported only in paclitaxel pretreated patients.

The safety, pharmacokinetics, and efficacy results of this study further support the proof of concept that coadministration of a P-gp / CYP3A4 inhibitor with a known drug substrate is feasible, safe, and able to improve the oral bioavailability of the substrate drug. Although both docetaxel formulations (i.e., ModraDoc001 capsule and ModraDoc006 tablet) explored in this study appear to show similar characteristics from a pharmacokinetics and a clinical point of view, the ModraDoc006 is preferred from a pharmaceutical point of view, as described by Sawicki and colleagues (6). For this reason, the ModraDoc006 formulation has been selected for further clinical development. Alternative dosing schedules of ModraDoc001 and ModraDoc006 have been explored in other recently published studies (22). Phase II studies with ModraDoc006 are currently ongoing.

Limitations of ModraDoc006/r in this once-daily schedule are that variability of systemic exposure to docetaxel after ModraDoc006/r is higher than of standard intravenous docetaxel, based on indirect comparison, and that ModraDoc006/r is associated with diarrhea that appears to be more frequent that what is common with intravenous docetaxel.

### Conclusion

Administration of the novel oral formulations of docetaxel as ModraDoc001 capsule and ModraDoc006 tablet in combination with ritonavir according to a once-weekly schedule is feasible and safe. The RP2D was determined as 60-mg ModraDoc001 capsule/100-mg ritonavir or 60-mg ModraDoc006 tablet/100-mg ritonavir. Toxicity appears manageable. Antitumor activity is considered promising. Further clinical investigation is warranted.

## Disclosure of Potential Conflicts of Interest

J.J. Moes and B. Nuigen are listed as coinventors on a patent about oral pharmaceutical taxane formulations, owned by The Netherlands Cancer Institute, Amsterdam and licensed to Modra Pharmaceuticals BV. J.H. Beijnen is an employee of and has ownership interests (including patents) at Modra Pharmaceuticals BV. J.H.M. Schellens is an employee of Modra Pharmaceuticals BV and is a consultant/advisory board member for Debiopharm. No potential conflicts of interest were disclosed by the other authors.

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# A Phase I Dose Escalation Study of Once-Weekly Oral Administration of Docetaxel as ModraDoc001 Capsule or ModraDoc006 Tablet in Combination with Ritonavir

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