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ARTICLE

Safety and pharmacokinetics of docetaxel in combination with pegvorhyaluronidase alfa in patients with non-small cell lung cancer

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Abstract

This open-label, phase Ib study (NCT02346370) assessed the effect of pegvorhyaluronidase alfa (PVHA; PEGPH20) on the plasma pharmacokinetics (PKs) and safety of docetaxel in 15 patients with stage IIIB/IV non-small cell lung cancer (NSCLC). The docetaxel PK profile from this study was consistent with simulations from a published docetaxel population PK model, and did not demonstrate an effect of PVHA on docetaxel PK. A maximum a posteriori Bayesian fit of the literature PK model to the docetaxel PK appeared unbiased. Adverse events (AEs) were generally consistent with previous reports for docetaxel monotherapy in NSCLC, except for higher incidence of musculoskeletal events, including myalgias, with PVHA plus docetaxel. The most common AEs were fatigue (87%), muscle spasms (60%), and myalgia (53%). Four patients experienced thromboembolic events (27%), three leading to treatment discontinuation. PVHA appeared to demonstrate an acceptable safety profile when given with docetaxel without significantly changing the plasma PK of docetaxel in patients with stage IIIB/IV NSCLC.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pegvorhyaluronidase alfa (PVHA; PEGPH20) enzymatically degrades hyaluronan (HA) in the tumor microenvironment, improving vascular perfusion and intratumoral delivery of anticancer agents. A phase III trial of PVHA in combination with other chemotherapeutic agents demonstrated improved tumor response rate in pancreatic adenocarcinoma, an HA-accumulating cancer type, compared with chemotherapy alone. However, it failed to demonstrate improvement in median overall survival.

WHAT QUESTION DID THIS STUDY ADDRESS?

This phase Ib study assessed the pharmacokinetics (PKs) and safety of combining PVHA with docetaxel, a common cytotoxic chemotherapy, in the treatment of patients

Clinical Trial ID: NCT02346370.

with stage IIIB/IV non-small cell lung cancer (NSCLC), another HA-accumulating cancer type.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Addition of PVHA did not result in new safety signals or measurably change the plasma PKs of docetaxel in patients with stage IIIB/IV NSCLC.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study suggests there is limited interaction, in terms of both plasma PKs and safety, between PVHA and docetaxel. The findings will inform further investigations of PVHA in combination with other small-molecule chemotherapy agents, such as gemcitabine.

INTRODUCTION

Pegvorhyaluronidase alfa (PVHA; PEGPH20) is a first-in-class biologic that potentially offers a novel approach to the treatment of cancer by targeting hyaluronan (HA), a naturally occurring glycosaminoglycan that can accumulate in many solid tumors.[1,2] Accumulation of HA can be associated with aggressive disease, cancer progression, metastasis, and poor prognosis.[3–7] The accumulation of HA in the tumor microenvironment (TME) can also cause increased tumor interstitial pressure, leading to compression of the tumor vasculature and impaired access of anticancer therapies to the tumor.[8–11]

The pharmacological actions, pharmacodynamics (PDs), and pharmacokinetics (PKs) of PVHA, as monotherapy or in combination with other anticancer agents, have been evaluated in multiple in vitro and in vivo preclinical models as well as in early clinical investigations.[2,9,10,12–16] PVHA enzymatically degrades HA and remodels the TME, reducing tumor interstitial pressure and improving vascular perfusion, thereby allowing increased access to the tumor and enhancing the antitumor activity of chemotherapeutic agents and immunotherapies.[2,10,11,15] Preclinical PKs and absorption, distribution, metabolism, and excretion (ADME) studies show a prolonged circulating half-life and biodistribution profile, as expected for a PEGylated enzyme.[15,17,18] Phase I data demonstrated that plasma concentrations of PVHA are proportional to the dose (without drug accumulation following multiple doses), indicating that single-agent PVHA is well-characterized by a linear, two-compartment PK model.[16] The half-life of PVHA in the plasma following administration of 3.0 μg/kg was ~ 1 day.[16] There was no significant change in the PK profile of PVHA when co-administered with gemcitabine.[16,19]

In a phase II randomized study in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (HALO 109–202; NCT01839487), PVHA combined with gemcitabine and *nab*-paclitaxel (PAG) was associated with modest but significantly improved ($p = 0.049$) median progression-free survival (PFS) compared with gemcitabine plus *nab*-paclitaxel (AG) alone (6.0 months for PAG vs. 5.3 months for AG; hazard ratio 0.73; 95% confidence interval 0.53–1.00).[20] The improvement in median PFS in the PAG versus AG arm of the phase II study was most pronounced in the subgroup that had HA-high tumors (median PFS for PAG and AG was 11.7 and 7.8 months, respectively).[20] However, a phase III trial failed to demonstrate an improvement in median overall survival in the PAG group compared with the AG group in patients with HA-high pancreatic ductal adenocarcinoma.[21]

Docetaxel is a common cytotoxic chemotherapeutic agent used for locally advanced or metastatic breast cancer, non-small cell lung cancer (NSCLC), hormone-refractory prostate cancer (with prednisone), gastric adenocarcinoma (with cisplatin and fluorouracil), and squamous cell carcinoma of the head and neck (with cisplatin and fluorouracil).[22] NSCLC accounts for 85% to 90% of lung cancer cases and is by far the leading cause of cancer-related deaths worldwide.[23–25] Until recently, docetaxel was used both in first-line platinum-based chemotherapy regimens and as a single agent in the second- or third-line treatment of advanced NSCLC.[24]

Preclinical studies with PVHA have shown antitumor effects in models of lung cancer and other malignancies,[18] and PVHA was shown to enhance the activity of docetaxel in tumors with high levels of HA.[15,26] This phase Ib clinical trial (HALO 107-201; NCT02346370) was therefore undertaken to investigate the activity of docetaxel plus PVHA in patients with recurrent, previously treated, locally advanced or metastatic NSCLC. It was originally designed as a two-stage study, comprising a dose-escalation phase to determine the recommended phase II dose (RP2D), and a dose-expansion phase in patients with HA-high tumors. However, the study was discontinued early during the dose-escalation stage as a result of changes in the treatment landscape for NSCLC, including the introduction of immune checkpoint inhibitors, such as nivolumab and pembrolizumab.[27,28] As

a consequence, docetaxel became a later-line therapy in the standard of care for NSCLC. Here, we compare the findings from the dose-escalation stage of the HALO 107-201 study with historical safety and PK data for docetaxel. Using simulations from a previously published PK model for docetaxel, together with the docetaxel PK profile from this study, we assessed whether the safety, tolerability, and PKs of docetaxel were affected by combination with PVHA.

METHODS

Study design

This phase Ib, multicenter, open-label study (HALO 107-201; NCT02346370) initiated in February 2015 included a dose-escalation period using a standard 3+3 dose-escalation design in patients with NSCLC, irrespective of HA levels. A cohort expansion period in patients with high levels of HA was planned to follow. The dose-escalation period aimed to evaluate the safety and tolerability of docetaxel and PVHA combination in patients with NSCLC, and to determine the RP2D. The cohort expansion period was intended to assess the safety, tolerability, preliminary efficacy (antitumor activity), and PK/PD profile of the docetaxel and PVHA combination in patients with high levels of HA. Due to the rapidly evolving standard of care for patients with NSCLC, whereby docetaxel became a later-line therapy, the study was discontinued in August 2016. Enrollment was stopped at that time, and ongoing patients continued study treatment until disease progression or unacceptable toxicity.

In the dose-escalation period, PVHA was administered i.v. on day 1 of a 21-day cycle at doses 1.6 μg/kg ($n = 7$), 2.2 μg/kg ($n = 4$), and 3.0 μg/kg ($n = 4$), and docetaxel was administered i.v. on day 2 of each cycle at standard dosing of 75 mg/m^2 for all patients ($n = 15$). The regimen and doses were based on initial clinical studies with PVHA,[16,19] and the recommended 3-weekly administration of docetaxel.[22] Docetaxel dose adjustments were permitted to manage adverse events (AEs). All patients received aspirin 81 mg once daily as prophylaxis for arterial thromboembolic (TE) events (unless they were on chronic anticoagulation therapy, which they continued), and dexamethasone (8 mg twice daily from day 1 to day 3 of each cycle) to reduce musculoskeletal events (MSEs), which are associated with PVHA treatment. Patients with a history of deep vein thrombosis (DVT) received enoxaparin 40 mg/day.

Patients

Eligible patients were greater than or equal to 18 years of age, with a life expectancy of greater than or equal to 3 months, and histologically confirmed, previously treated Stage IIIB or IV NSCLC, who had failed one previous platinum-containing chemotherapy regimen for locally advanced or metastatic disease and had, in total, no more than three anticancer regimens. Patients were also required to have the following clinical laboratory values at screening: total bilirubin less than or equal to 1.5 × upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase less than or equal to 2 × ULN (<5 × ULN was allowed if liver metastases were present); serum creatinine less than or equal to 1.5 mg/dL or calculated creatinine clearance greater than or equal to 60 mL/min; serum albumin greater than or equal to 3.0 g/dL; hemoglobin greater than or equal to 10 g/dL; absolute neutrophil count greater than or equal to 1500 cells/mm^3; and platelet count greater than or equal to 100,000/mm^3. Key exclusion criteria included: previous docetaxel treatment; New York Heart Association class III or IV cardiac disease, myocardial infarction in the previous year, or pre-existing atrial fibrillation; history of cerebrovascular accident, transient ischemic attack, carotid artery disease, DVT with contraindication to anticoagulant drugs, or pulmonary embolism; another primary cancer within the last 3 years requiring treatment, except non-melanoma skin cancer, early-stage prostate cancer, or curatively treated cervical carcinoma in situ; known unstable brain metastases; infection requiring systemic therapy; and pregnant or breastfeeding women.

Sample collection

Plasma samples to assess the PKs of docetaxel were collected during the dose-escalation period of the study at the following time points: 30 (±5) min after the start and 30 (±5) min after termination of the docetaxel i.v. infusion on day 2 of cycles 1–3; at 4–6 h and 24 h following termination of the docetaxel i.v. infusion on day 2 of cycle 1 only; and at the end of each 21-day cycle (~504 h post dose). Plasma docetaxel concentrations were determined using a validated method using high-performance liquid chromatography with tandem mass spectrophotometry detection.[29] The lower limit of quantification for plasma docetaxel was 0.5 μg/L. The linear calibration range was from 0.5 to 100 μg/L.

Pharmacokinetic and maximum a posteriori probability-Bayesian analysis

For the docetaxel PK analysis, a previously developed population PK model using PK data from 547 patients with cancer (26 patients from two phase I studies and 521 patients from 22 phase II studies) was utilized (Figure S1).[30] This model characterized docetaxel PK as stationary and was described using a linear three-compartment mammillary PK model (see

Supplementary Text for details). This model, together with the patient and dosing regimen data from the current study, was used to perform Monte Carlo simulations to generate a median and 90% prediction interval for plasma docetaxel concentrations over time for the visual predictive check plots.

A maximum a posteriori (MAP)-Bayesian estimation was also performed using the prior population PK model for docetaxel[30] to identify any deviation from prior expectations and as a means for generating individual post hoc exposures for each participant. The prior population PK model was applied directly to the observed docetaxel PK data from the current study with all model parameters and the variance–covariance matrix fixed to the prior estimates. Goodness-of-fit for the MAP-Bayesian analysis was assessed by graphical examination of standard diagnostic and population analysis plots, and evaluation of individual and aggregate post hoc PK parameter estimates relative to known PKs of docetaxel. Further details of visual predictive checks and MAP-Bayesian analysis can be found in the Supplementary Text.

Safety

Safety was evaluated in all patients who received at least one dose of docetaxel and PVHA ($n = 15$). All dose-limiting toxicities (DLTs), AEs, serious AEs (SAEs), treatment discontinuations due to AEs, and deaths that occurred during the study were summarized for docetaxel plus PVHA. The relationship of AEs with each individual agent as assessed by the investigator was also summarized. The Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 was used to code AEs, which were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. DLTs were defined as any treatment-emergent AE of grade greater than or equal to 3 considered related to either study drug, except for grade 3 nausea, vomiting, or diarrhea lasting less than 5 days; asymptomatic grade 3 neutropenia; or grade 4 neutropenia lasting less than 7 days.

AEs observed in the current study were compared with those reported for docetaxel monotherapy in two randomized, controlled trials conducted in patients with advanced NSCLC (TAX 317 and TAX 320), as summarized in the prescribing information for docetaxel.[22,31,32]

Study oversight

This study was conducted in the United States under a Food and Drug Administration Investigational New Drug Application, and in accordance with the Declaration of Helsinki and Good Clinical Practice, and Guidelines of the International Conference on Harmonization. The study protocol received approval from the institutional review boards prior to study initiation, and any amendments were reviewed and approved thereafter.

RESULTS

Patient population

Prior to the August 2016 study discontinuation, 16 patients were enrolled, of whom 15 were treated with PVHA plus docetaxel in the dose-escalation stage (Figure S2). One patient experienced disease progression prior to initiation of treatment and was excluded from the study. Baseline demographics and clinical laboratory parameters are summarized in Table 1. The mean (SD) age of patients was 62.6 (9.0) years, 67% were women, and 73% were White. All patients had a hepatic function composite score of 0 (see Supplementary Text). As enrollment stopped during dose escalation, the RP2D could not be determined and the cohort expansion stage was not initiated.

A total of 70 plasma samples were available from 15 patients enrolled in the study. Of these, 42 samples were included in the PK analyses, utilizing actual PK sample collection times: seven, 31, two, and two samples were collected at 0.5, 1.5, 6, and 24 h, respectively, after the start of the docetaxel infusion when grouped by scheduled PK sample collection time. Plasma samples were collected during treatment cycles 1–3, with 48% of samples used in PK analyses from cycle 1. Of the original 70 samples, 16 were excluded as predose samples. A further five samples from five patients with reportable docetaxel concentrations towards the end of the 21-day cycle (one sample at an unscheduled end-of-treatment time of 286 h, and four samples at 504 h) were excluded from the analysis because the concentrations would have been unquantifiable based on the terminal-phase half-life of docetaxel (reported as 11.4 h);[30] this indicated that there was a potential data-recording error (i.e., the samples were likely to have been collected after, rather than before, dosing in the next cycle). Docetaxel concentrations were below the lower limit of quantification of the assay (0.5 μg/L) at the end of the cycle for an additional seven samples; these samples were retained in the PK analysis dataset but excluded from the MAP-Bayesian estimation (using OMIT = 1 coding in the analysis dataset).

Docetaxel population PK analysis

The visual predictive check showed that the observed plasma docetaxel concentration–time data were in good agreement with the median and were generally within the 5th and 95th percentiles of the simulated plasma docetaxel concentration–time data over the first 36 h after docetaxel dosing, with the

TABLE 1 Baseline demographics and clinical laboratory parameters (PK analysis population)

	Total ($N = 15$)
Age, years	
Mean (SD)	62.6 (9.0)
Median (range)	63.0 (48–74)
Weight, kg	
Mean (SD)	68.9 (12.7)
Median (range)	70.5 (38.0–89.4)
Height, cm	
Mean (SD)	164.0 (10.2)
Median (range)	164 (145–185)
BSA, m^2	
Mean (SD)	1.75 (0.21)
Median (range)	1.78 (1.26–2.01)
BMI, kg/m^2	
Mean (SD)	25.5 (3.4)
Median (range)	25.6 (17.6–30.8)
Gender, *n* (%)	
Male	5 (33.3)
Female	10 (66.7)
Race	
White	11 (73.3)
Other	4 (26.7)
Albumin (g/L)	
Mean (SD)	43.5 (4.7)
Median (range)	45 (31–50)
α_1-acid glycoprotein (g/L)[a]	
Mean (SD)	1.51 (0.39)
Median (range)	1.46 (0.63–2.40)
ALT (U/L)	
Mean (SD)	28.5 (22.3)
Median (range)	23 (10–105)
AST (U/L)	
Mean (SD)	29.7 (15.1)
Median (range)	29 (8–73)
ALP (U/L)	
Mean (SD)	105 (47.5)
Median (range)	100 (45–213)
HEP1, *n* (%)	1 (7.7)
HEP2, *n* (%)	0 (0)
HEP12, *n* (%)	0 (0)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; HEP1, hepatic function score related to ALT or AST elevation >60 U/L; HEP2, hepatic function score related to ALP elevation >300 U/L; HEP12, hepatic function composite score related to both: (1) ALT or AST elevation >60 U/L and (2) ALP elevation >300 U/L; PK, pharmacokinetic.

[a]Measurements for α1-acid glycoprotein were added as a protocol amendment, and so were available in only four of 15 patients; the median value of 1.46 g/L was instead utilized for all patients missing this covariate.

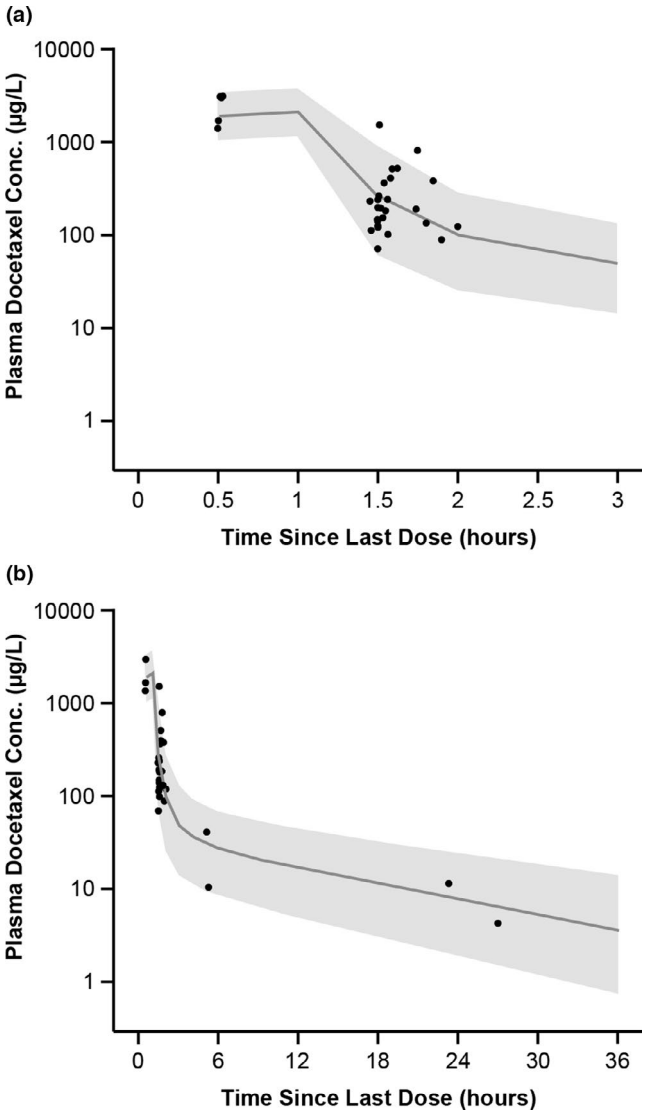

FIGURE 1 Visual predictive check for the plasma docetaxel concentration–time data at 0–3 h (a) and 0–36 h (b) post dose. Docetaxel was administered at the standard dose of 75 mg/m^2 infused i.v. Circles represent the observed docetaxel concentrations; the line and shaded region represent the median and 90% prediction interval for the simulated docetaxel data using the prior population pharmacokinetic model and the same dosing histories and demographic characteristics as the patients in the current study

majority of available data collected during the early distribution phase 0–3 h after dosing (Figure 1). A MAP-Bayesian fit of the prior population PK model[30] for docetaxel to the observed data from this study was unbiased (Figure 2), and there was reasonable agreement between the observed plasma docetaxel concentrations and the population predictions ($r^2 = 0.77$) as well as the individual post hoc predictions ($r^2 = 0.96$). There were also no apparent trends between the residuals and the population predictions, time since last dose, or with docetaxel dose level, which would indicate model misspecification or deviation from linear or dose-proportional PK. Table 2 shows summary statistics for individual post

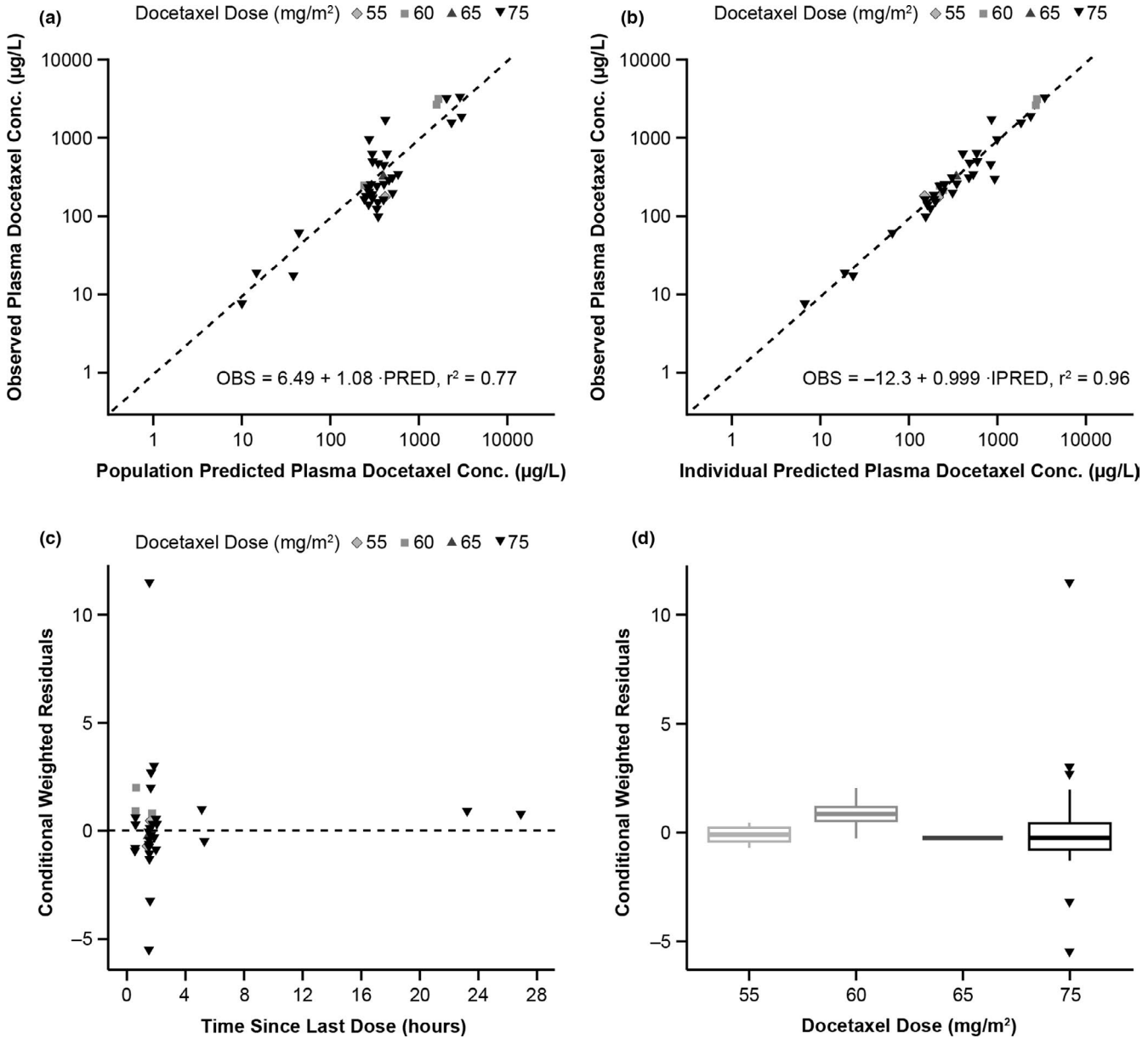

FIGURE 2 Goodness-of-fit plots for the MAP-Bayesian fit of the prior population PK model for docetaxel to the observed plasma docetaxel concentration–time data from patients with non-small cell lung cancer (a, b), and conditional population-weighted residuals versus time since last docetaxel dose (c) and docetaxel dose (d). IPRED, individual predicted; MAP, maximum a posteriori; OBS, observed; PK, pharmacokinetic; PRED, predicted

hoc PK parameters and derived exposures for cycle 1, during which all patients received docetaxel 75 mg/m^2 by i.v. infusion over ~ 1 h. The observed mean (SD) clearance and steady-state volume of distribution for docetaxel were 36.7 (9.9) L/h and 145 (31.8) L, compared with means of 36.7 L/h and 149 L for docetaxel alone in the prior PK model.

Safety and tolerability

The most frequent any-grade (grade ≥3) AEs in the docetaxel monotherapy pivotal trials in NSCLC (TAX 317 and TAX 320) combined[22] and the corresponding rates in the current study of docetaxel plus PVHA were as follows: alopecia 56% versus 13%; anemia 91% versus 7% (grade ≥3: 9% vs. 0%); asthenia 53% versus 87% (grade ≥3: 18% vs. 7%); leukopenia 84% versus 0% (grade ≥3: 49% vs. 0%); and neutropenia 84% versus 40% (grade ≥3: 65% vs. 40%; Table 3).

In the current study, all 15 patients received at least one dose of PVHA and docetaxel; PVHA was administered at 1.6 µg/kg (n = 7), 2.2 µg/kg (n = 4), and 3.0 µg/kg (n = 4; Figure S2). The mean (SD) number of doses administered for both treatments was 4.1 (3.2). Median treatment duration was 83 days for PVHA and 82 days for docetaxel. During

TABLE 2 Summary statistics of post hoc PK parameters and derived exposures for cycle 1 when all patients received i.v. docetaxel 75 mg/m^2

	T_{max} (h)	C_{max} (μg/L)	$AUC_{0-\infty}$ (μg•h/L)	CL (L/h)	V_c (L)	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{13} (h^{-1})	k_{31} (h^{-1})	V_{p1} (L)	V_{p2} (L)	V_{ss} (L)
Mean[a]	1.12	2500	3820	36.7	8.12	1.07	1.67	1.32	0.08	5.43	132	145
SD[a]	0.17	569	970	9.92	2.34	N/A	0.48	0.22	0.001	1.72	29.3	31.8

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 to infinity; CL, clearance; C_{max}, maximum plasma concentration; k_{12}, first-order rate-constant for transfer from the central to the first peripheral compartment; k_{13}, first-order rate-constant for transfer from the central to the second peripheral compartment; k_{21}, first-order rate-constant for transfer from first peripheral compartment to the central compartment; k_{31}, first-order rate-constant for transfer from the second peripheral compartment to the central compartment; NA, not applicable; PK, pharmacokinetic; T_{max}, time when C_{max} occurred; V_c, central volume of distribution; V_p, peripheral volume of distribution; V_{ss}, steady-state volume of distribution.

[a]Geometric means and SDs are presented for all parameters except T_{max}, for which the arithmetic mean and SD are presented as T_{max} does not have a log-normal distribution.

cycle 1, DLTs were evaluated in 13 of 15 patients. Two of the four patients who received 3.0 μg/kg PVHA experienced four DLTs altogether: one had grade 3 neutropenia, grade 4 gastroenteritis due to *Escherichia coli*, and grade 4 sepsis, and the other patient had a grade 3 DVT. One patient who received 2.2 μg/kg PVHA experienced one DLT (grade 2 DVT). All DLTs were considered by the investigator as possibly related to treatment. No DLTs occurred in the seven patients who received 1.6 μg/kg PVHA. The highest tolerated dose of PVHA evaluated up to study discontinuation was 2.2 μg/kg.

All 15 patients experienced at least one all-cause AE (any grade), with grade greater than or equal to 3 AEs reported in 80% of patients. The most common all-cause any-grade AEs were fatigue (87%), muscle spasms (60%), and myalgia (53%; Table 4). The most common any-grade drug-related AEs were muscle spasms (60%), myalgia (47%), and fatigue (47%) for PVHA, and fatigue (67%), muscle spasms (33%), and neutropenia (33%) for docetaxel. A total of seven (46.7%) patients experienced at least one grade greater than or equal to three PVHA-related AE. Among these, neutropenia was the only grade greater than or equal to3 AE related to PVHA to be reported in at least two patients. One patient had a grade 1 AE of increase in hepatic enzyme based on the composite score for hepatic function utilized in the population PK analysis (see Supplementary Text).

SAEs were reported in seven patients, four of whom experienced SAEs related to PVHA: one patient with grade 3 neutropenia, grade 4 gastroenteritis due to *E. coli*, and grade 4 sepsis, and one patient with grade 3 DVT in the 3.0 μg/kg cohort; one patient with pericardial effusion in the 2.2 μg/kg cohort; and one patient with grade 2 myalgia in the 1.6 μg/kg cohort. Five SAEs considered related to docetaxel were recorded and distributed among three patients (neutropenia, pericardial effusion, gastroenteritis due to *E. coli*, sepsis, and DVT). There were no AEs with an outcome of death; all five deaths reported during the study were due to disease progression.

Four AEs led to discontinuation of study drug in four patients. Three of these patients experienced TE events considered by the investigator to be possibly related to PVHA (grade 2 DVT) or both PVHA and docetaxel (grade 3 DVT and grade 2 superficial thrombophlebitis). The fourth patient who discontinued treatment had breast cellulitis (considered unrelated to study drug) and peripheral sensory neuropathy (considered related to docetaxel). A fourth TE event (grade 2 DVT), which did not lead to discontinuation, was also considered by the investigator as possibly related to PVHA. Overall, MSEs occurred in 14 patients (93.3%); these were predominantly grade 1/2 in severity and were mostly muscle spasms or myalgia. All but one MSE (a case of myalgia) were considered related to PVHA.

DISCUSSION

PVHA is a novel, first-in-class, HA-targeting biologic with emerging PK, safety, and efficacy clinical data in numerous oncology indications, in combination with a range of therapeutic agents. This two-stage phase Ib study in patients with NSCLC was initiated to assess the safety and tolerability of PVHA combined with docetaxel, to determine the RP2D of PVHA in the dose-escalation stage, and then to assess the safety and tolerability of the combination in patients with HA-accumulating tumors in the dose-expansion stage. The study was discontinued early due to changes in the recommended management of advanced NSCLC.[33]

Model-based methodologies, such as the MAP-Bayesian approach combined with population PK analysis, and comparison of safety findings with historic large-scale trials, were applied in this study and add to the ongoing assessment of the safety and PKs of chemotherapy when combined with PVHA. The PK analyses indicated that PVHA does not appear to affect the PKs of docetaxel. The observed plasma docetaxel concentration–time data were consistent with the median, and were generally within the 5th and 95th percentiles of the simulated plasma docetaxel concentration–time data over the first 36 h after a dose of docetaxel. Moreover, the MAP-Bayesian fit of the docetaxel population PK model[30] to the observed plasma docetaxel concentration–time data from the current study was unbiased, with no apparent model misspecification or deviation from the expected PK profile. The published and validated docetaxel PK model was based on data from 22 phase II trials involving

TABLE 3 Most frequent all-cause AEs in the docetaxel monotherapy pivotal trials (TAX 317 and TAX 320)[22] and the corresponding rates in the current study with docetaxel plus PVHA

	PVHA dose level + docetaxel ($N = 15$)								Docetaxel 75 mg/m^2 monotherapy ($N = 176$)	
	1.6 µg/kg ($n = 7$)		2.2 µg/kg ($n = 4$)		3.0 µg/kg ($n = 4$)		Total ($N = 15$)			
AE, *n* (%)[a]	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades
Alopecia	0	2 (29)	0	0	0	0	0	2 (13)	0	99 (56)
Anemia	0	0	0	1 (25)	0	0	0	1 (7)	16 (9)	160 (91)
Asthenia (fatigue)	1 (14)	6 (86)	0	4 (100)	0	3 (75)	1 (7)	13 (87)	32 (18)	93 (53)
Diarrhea	1 (14)	1 (14)	0	1 (25)	0	2 (50)	1 (7)	4 (27)	5 (3)	40 (23)
Febrile neutropenia	0	0	0	0	0	0	0	0	11 (6)	11 (6)
Fluid retention[b]	0	3 (43)	1 (25)	2 (40)	0	0	1 (7)	5 (33)	5 (3)	60 (34)
Hypersensitivity reactions	0	0	0	0	0	0	0	0	5 (3)	11 (6)
Infection	2 (29)	3 (43)	0	1 (25)	1 (25)	2 (50)	3 (20)	6 (40)	18 (10)	60 (34)
Leukopenia	0	0	0	0	0	0	0	0	86 (49)	148 (84)
Musculoskeletal events	1 (14)	6 (86)	0	4 (100)	1 (25)	4 (100)	2 (13)	14 (93)	NG	NG
Myalgia	0	4 (57)	0	1 (25)	0	3 (75)	0	8 (53)	0	11 (6)
Arthralgia	0	2 (29)	0	0	0	0	0	2 (13)	0	5 (3)
Nail disorder	0	0	0	1 (25)	0	0	0	1 (6.7)	1 (1)	19 (11)
Nausea	0	3 (43)	0	0	0	2 (50)	0	5 (33)	9 (5)	60 (34)
Neuromotor	0	0	0	0	0	0	0	0	9 (5)	28 (16)
Neurosensory (nervous system disorders)	1 (14)	5 (71)	0	2 (50)	0	1 (25)	1 (7)	8 (53)	4 (2)	40 (23)
Neutropenia	1 (14)	1 (14)	1 (25)	1 (25)	3 (75)	3 (75)	5 (33)	5 (33)	114 (65)	148 (84)
Pulmonary (respiratory, thoracic and mediastinal disorders)	2 (29)	6 (86)	0	3 (75)	1 (25)	3 (75)	3 (20)	12 (80)	37 (21)	72 (41)
Skin (skin irritation and rash erythematous)	0	1 (14)	0	0	0	1 (25)	0	2 (13)	2 (1)	35 (20)
Stomatitis	0	0	0	0	0	1 (25)	0	1 (7)	4 (2)	46 (26)
Taste perversion (dysgeusia)	0	0	0	0	0	1 (25)	0	1 (7)	2 (1)	11 (6)
Thrombocytopenia	0	1 (14)	0	0	0	1 (25)	0	2 (13)	5 (3)	14 (8)
Treatment-related mortality	0	0	0	0	0	0	0	0	NA	4 (3)
Vomiting	0	1 (14)	0	1 (25)	0	2 (50)	0	4 (27)	5 (3)	39 (22)

Patients are only included once, even if they experience multiple events in a particular category.

Abbreviation: AE, adverse event; NA, not applicable; NG, not grouped; PVHA, pegvorhyaluronidase alfa.

[a]Terms used in the docetaxel prescribing information with equivalents used in the current study in parentheses (where they differ).[22]

[b]Fluid retention includes edema (peripheral, localized, generalized, lymphedema, pulmonary edema, edema otherwise not specified) and effusion (pleural, pericardial, and ascites).[22] The numbers of AEs for docetaxel monotherapy are calculated based on the percentage values.

TABLE 4 Summary of AEs

	PVHA dose level +docetaxel ($N = 15$)							
	1.6 μg/kg ($n = 7$)		2.2 μg/kg ($n = 4$)		3.0 μg/kg ($n = 4$)		Total ($N = 15$)	
AE category, *n* (%)	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**	**All grades**
AEs	5 (71)	7 (100)	3 (75)	4 (100)	4 (100)	4 (100)	12 (80)	15 (100)
Serious AEs	2 (29)	3 (43)	1 (25)	1 (25)	3 (75)	3 (75)	6 (40)	7 (47)
AEs leading to discontinuation	1 (14)	1 (14)	0	2 (50)	1 (25)	1 (25.0)	2 (13)	4 (27)
Treatment-related AEs	3 (43)	7 (100)	3 (75)	4 (100)	4 (100)	4 (100)	10 (67)	15 (100)
Related to PVHA	1 (14)	6 (86)	3 (75)	4 (100)	3 (75)	4 (100)	7 (47)	14 (93)
Related to docetaxel	3 (43)	7 (100)	3 (75)	4 (100)	4 (100)	4 (100)	10 (67)	15 (100)
All-cause AEs of special interest								
Thromboembolic events	0	0	0	3 (75)	1 (25)	1 (25)	1 (7)	4 (27)
Musculoskeletal events	1 (14)	6 (86)	0	4 (100)	1 (25)	4 (100)	2 (13)	14 (93)

Abbreviations: AE, adverse event; PVHA, pegvorhyaluronidase alfa.

Numbers and proportions represent the number of patients. Patients are only included once, even if they experience multiple events in a particular category.

patients with a variety of tumor types, including NSCLC,[30] justifying the comparison between the PKs in the current study and the historical model. A MAP-Bayesian approach was adopted due to the sparse sampling and small population size in order to obtain further individual post hoc PK parameters for each patient. Other clinical studies have used this docetaxel population PK model, with or without Bayesian methodology, to determine the effects of combination with other therapies on the PKs of docetaxel in a range of solid tumors.[34–36] The lack of effect of PVHA on docetaxel PKs is not unexpected following preclinical research demonstrating that PVHA had no measurable effect on the plasma PKs of other small-molecule anticancer agents, including gemcitabine in a mouse model of pancreatic cancer[2] and eribulin in triple-negative breast cancer xenografts.[37] These preclinical studies also showed that PVHA enhanced intratumoral exposure to the small-molecule anticancer therapies.

The safety profile of PVHA plus docetaxel reported here was consistent with the safety profiles for the individual agents established in previous clinical trials.[16,22,38] The majority of AEs attributed to PVHA were MSEs, only one of which, a case of grade 2 myalgia, was categorized as serious. Docetaxel-related AEs were typical of those previously reported across different malignancies, and consistent with two large phase III monotherapy clinical trials of docetaxel 75 mg/m^2 ($n = 176$; TAX 317 and TAX 320) in patients with unresectable locally advanced NSCLC previously treated with platinum-based chemotherapy.[22] The rates of AEs reported with PVHA plus docetaxel were therefore generally similar to those reported for single-agent docetaxel,[22] with the exception of the higher incidence of MSEs reported with PVHA (myalgia: 53%) in comparison with single-agent docetaxel (myalgia: 6%).[22] A total of four TE events were reported, one in each of four patients (27%), of which two events were considered by the investigator as possibly related to PVHA treatment and two as possibly related to both PVHA and docetaxel. A similar rate (29%) was reported in a study of PVHA in combination with AG in metastatic pancreatic cancer,[38] but the rate was only 2% in two phase I monotherapy studies conducted in a range of cancers.[16] Hence, with no directly comparable data from other studies in similar patients and only a small population sample, the TE findings from the present study should be interpreted with caution. Enoxaparin prophylaxis for TEs reduced the incidence of TEs in the phase II PVHA clinical trial in pancreatic cancer and resulted in low TE rates in the phase III trial in patients with metastatic pancreatic cancer,[21,32] but it is not yet clear whether enoxaparin prophylaxis reduces the rate of TEs associated with PVHA in other cancers.

Although the PK and safety findings in this phase Ib study were similar to historical docetaxel data, there are limitations to this analysis. First, the sample size of the phase Ib study was much smaller than planned and compared with that of the historic docetaxel dataset, and so did not allow for a very robust statistical comparison for safety endpoints. The historic comparison is also limited by the different study designs (phase I vs. phase III). Second, five samples from five patients had quantifiable amounts of docetaxel in plasma samples that had been collected toward the end of the 21-day cycle, whereas the concentration of docetaxel in the other samples at this time point was below the assay lower limit of quantification. Given that the terminal-phase half-life of docetaxel is reported as less than 12 h,[30] these data points may have resulted from a data-recording error; it is likely that the sample was collected after administering the next scheduled dose of docetaxel rather than before. Therefore, the five quantifiable measurements towards the end of the 21-day cycle were not included in the PK analysis. Another possible limitation of the study design is that the 4–6- and 24-h postdose samples for PK analysis were collected

only in cycle 1 of treatment. It should also be noted that the prior population PK model for docetaxel was constructed using data collected within 24 h after dose administration.[30] Hence, although unlikely, the possibility of a more prolonged terminal elimination phase resulting from the return of docetaxel from a more slowly equilibrating compartment cannot be excluded. Finally, most of the observed plasma docetaxel concentration–time data from the study were determined using only a small number of samples collected during the alpha- and beta-elimination phases within 2 h after dosing and, therefore, it is possible that the current data may not allow for accurate detection of alterations in docetaxel clearance. However, although a lack of late elimination phase samples may result in high statistical shrinkage and impede accurate estimation of docetaxel clearance and area under the curve, the use of the MAP-Bayesian fit will have precluded any impact of shrinkage on the estimation. Hence, the MAP-Bayesian fit of the prior population PK model for docetaxel should reflect the observed data from this study in an unbiased way.

Overall, results show that the plasma PKs of the small-molecule agent docetaxel were not measurably changed when given in combination with PVHA, and confirm the lack of new safety signals when PVHA was combined with docetaxel in patients with previously treated stage IIIB/IV NSCLC. These findings may have relevance to combinations with other small-molecule chemotherapy agents such as gemcitabine, paclitaxel, or the constituents of FOLFIRINOX.[18] This analysis approach offers an efficient method of evaluating combination regimens of PVHA and other anticancer agents that have established safety findings and validated population PK models.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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CONFLICT OF INTEREST

T.H., D.C.M., R.E.S., C.N., and A.M.F. are former employees of Halozyme Therapeutics, Inc., and T.H., D.C.M., and R.E.S. hold shares in the company. D.E.M. and S.A.V.W. are employees of Enhanced Pharmacodynamics, LLC. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. A.M.F., C.N., D.C.M., and R.E.S. designed the research. M.B., N.G., A.M.F., C.N., S.A.V.W., and D.E.M. performed the research. T.H., A.M.F., C.N., S.A.V.W., and D.E.M. analyzed the data. A.M.F., C.N., and R.E.S. contributed new analytical tools.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

DATA SHARING STATEMENT

Halozyme Therapeutics, Inc. follows policies established by the International Committee of Medical Journal Editors. The studies were conducted by Halozyme Therapeutics, Inc., and the data are held by the company. Additional information about the studies and/or datasets can be obtained by contacting Halozyme Therapeutics, Inc.: 11388 Sorrento Valley Road, San Diego, CA 92121, USA; Phone: +1.858.794.8889; Email: publications@halozyme.com

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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