

## A Phase I First-in-Human Pharmacokinetic and Pharmacodynamic Study of Serdemetan in Patients with Advanced Solid Tumors

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### Abstract

**Purpose:** Originally isolated on the basis of its ability to induce p53, serdemetan showed potent activity in various preclinical models, inducing S-phase arrest and apoptosis in *TP53* wild-type and mutant tumors. This study evaluated the safety and tolerability of serdemetan, determined the pharmacokinetic and pharmacodynamic profiles, and identified a recommended phase II dose.

**Patients and Methods:** Patients (71) with refractory solid tumors were allocated to dose-escalating cohorts (3+3 patients each) and received oral serdemetan once daily in 21-day cycles to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT). Plasma was collected for pharmacokinetic analyses. Paired baseline and on-treatment skin and tumor biopsies were done; blood samples were collected for pharmacodynamic analyses, including p53 and macrophage inhibitory cytokine-1 induction.

**Results:** The MTD of serdemetan was determined to be 350 mg once daily. During this study, grade 3 QTc prolongation was the most common DLT and nausea (66.2%) was the most frequent treatment-emergent adverse event. Serdemetan was rapidly absorbed after oral administration and exhibited dose-proportional pharmacokinetics. At steady state, mean maximum plasma concentration ( $C_{max}$ ) was 2,330 ng/mL and mean area under plasma concentration curve ( $AUC_{0-24h}$ ) was 43.0  $\mu\text{g}\cdot\text{h}/\text{mL}$ , with serdemetan 300 mg/d. There was a dose- and exposure-dependent p53 induction. One patient with breast cancer showed a partial response; 22 (38.6%) patients had stable disease.

**Conclusions:** Serdemetan treatment was associated with p53 induction in both tumor and surrogate tissue pharmacodynamic studies and modest clinical activity. Although serdemetan was well tolerated with dose-proportional pharmacokinetics, exposure-related QTc liability was observed. *Clin Cancer Res*; 17(19); 6313–21. ©2011 AACR.

### Introduction

Tumor suppressor proteins act through a variety of mechanisms to control the process of cell proliferation, including suppression of cell division, induction of apoptosis, and identification and repair of damaged DNA (1). Deactivation of the tumor suppressor protein p53 is critical for the development of many tumors (2). Serdemetan

(JNJ-26854165) is a novel tryptamine derivative that was originally isolated in a p53-activating screen designed to detect increased cellular expression of p53. Whereas initial studies suggested activity as an inhibitor of human double minute-2 oncogene (HDM2), subsequent studies showed antiproliferative activity in both *TP53* wild-type and mutant tumor models, with equivalent potencies regardless of p53 status (3). Serdemetan inhibits proliferation of cell lines

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

Data from this study were presented at the 20th EORTC-NCI-AACR Symposium on "Molecular Targets and Cancer Therapeutics", October

21 to 24, 2008, Geneva, Switzerland; the 45th Annual Meeting of the American Society of Clinical Oncology, May 29 to June 2, 2009, Orlando, Florida; and the 46th Annual Meeting of the American Society of Clinical Oncology, June 4 to 8, 2010, Chicago, Illinois.

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doi: 10.1158/1078-0432.CCR-11-1101

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### Translational Relevance

This first-in-human study described the safety profile and the maximum tolerated dose (MTD) of serdemetan, a novel tryptamine derivative initially characterized as a p53 inducer agent, in patients with advanced stage/refractory solid tumors. Extensive pharmacodynamic (PD) and pharmacokinetic (PK) analyses, as well as PK/PD modeling, helped to identify a minimal biologically effective dose. The MTD of serdemetan was 350 mg. PD analyses of paired baseline and on-treatment skin and tumor biopsies provided evidence of p53 induction. There was a dose-related increase in p53 induction in skin biopsies at doses  $\geq 150$  mg/d. Evidence existed for an exposure–effect relationship for p53 induction in skin biopsies. Outcomes of PD assays from skin and tumor biopsies were concordant in several patients. Due to exposure-related QTc toxicity observed with serdemetan, the development of derivatives lacking this liability is currently under consideration.

derived from multiple solid tumor types, with IC<sub>50</sub> in the low micromolar range, and has shown potent *in vivo* anti-tumor activity in non–small cell lung, breast, colon, prostate, and glioblastoma cancer xenograft models. It induced p53-mediated apoptosis in acute leukemia cells with wild-type *TP53* (3). Microarray analysis of a wild-type *TP53* tumor cell line response to various anticancer drugs showed that serdemetan induces a gene expression profile similar to that of chemotherapeutic agents known to interfere with DNA synthesis and induce S-phase arrest (3). Although the exact mechanism of action remains under investigation, the observed activities of serdemetan in preclinical models suggest that it may have efficacy in the treatment of cancer.

The primary objectives of this first-in-human, phase I study were to explore the safety and pharmacokinetic (PK) profiles of serdemetan, and to determine its dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) in patients with advanced malignancies. A key secondary objective was to explore the pharmacodynamic (PD) effects on the p53-dependent pathways in sequential tumor and skin biopsies, as well as in blood samples, to better characterize the recommended phase II dose for further development.

### Patients and Methods

#### Study population

Patients of either sex, 18 years or older, with advanced, refractory solid malignancies were eligible for the study. All patients were required to have histologic or cytologic confirmation of malignancy, an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less and adequate bone marrow, liver, and renal function.

Patients were excluded from the study if they had central nervous system (CNS) metastasis, uncontrolled heart dis-

ease or hypertension, or psychiatric illness incompatible with study participation. After the initial instances of QTc prolongation were observed, stricter criteria excluding patients at increased risk for QTc prolongation (clinically significant rhythm or conduction abnormality, congenital long QT syndrome, QTc of more than 450 msec at screening, structural heart disease, liver impairment, and family history of long QT syndrome, or sudden death before age 40 years) were introduced by protocol amendment. Recent, ongoing, or expected medical therapy with amiodarone or warfarin excluded patients from participation in the study.

An Independent Ethics Committee at each study site approved the protocol. This study was conducted in accordance with the Declaration of Helsinki, consistent with good clinical practices and applicable regulatory requirements. All patients provided written informed consent to participate in the study. A Data Review Committee (DRC) was installed to ensure optimum study conduct.

#### Study design

This phase I study was conducted from December 2006 to February 2010 at 5 study centers in Belgium and Spain. It included a 14-day screening phase, an open-label treatment phase consisting of 21-day cycles, and an end-of-study visit within 14 days after the last dose.

The study was divided into 2 parts, a dose-escalation phase (part 1) and an expansion phase (part 2). Serdemetan was administered orally, starting with a 4 mg/d dose, with subsequent doses escalated in a 3+3 dose escalation scheme, to determine the MTD. The starting dose was initially calculated at 8 mg, on the basis of the human equivalent dose of one-sixth of the lowest dose in the rat (the most sensitive species) that does not cause severe irreversible toxicity, whereas daily dosing was deemed optimal for a proposed HDM2 inhibitor. The starting dose was subsequently reduced to 4 mg daily, at the request of Belgium Health Authorities. Up to 3 additional patients were added if 1 patient exhibited a DLT within the first cycle of therapy (DLT period). Further dose escalation was halted if at least 2 of a maximum of 6 patients within a cohort exhibited a DLT. Inpatient dose escalations were allowed to minimize early cohort exposure to subtherapeutic doses.

To minimize exposure of patients to dose levels predicted to lack therapeutic potential, a pharmacokinetically guided dose escalation (4, 5) was initially pursued, in which dose increments of up to 500% were allowed. Once the drug–drug interaction safe level of 50 ng/mL maximum plasma concentration ( $C_{max}$ ) had been achieved, an adapted "modified Fibonacci" scheme (6, 7) was pursued, in which dose increases of 10% to 100% were allowed. The DRC convened after every dose cohort had completed the DLT period, and at additional time points if necessary, to review all available safety, PK, and PD data. If unacceptable toxicity occurred in patients after the DLT period, dose deescalations were permitted.

During part 2 of the study, additional patients were enrolled to increase the number of patients evaluated for safety, PK, and PD profiles of serdemetan, at doses and

schedules that were candidates for phase II studies. At least 12 evaluable patients for each dose or schedule were to be investigated.

During cycle 1, study investigations (PK, PD, and toxicity assessments) were carried out on days -1, 1, 3, 7, 10, 14, and 21; interim safety evaluations were done on days 3, 7, 10, and 14. Interim safety evaluations were done on days 3, 10, and 21 of cycle 2 and on day 21 of subsequent cycles. During cycle 2, PD sampling was carried out on day 21. Tumor response assessments were done on day 21 of every alternate treatment cycle from cycle 2 onwards.

Serdemetan solution (Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen Pharmaceutical, N.V.) was supplied in 3 concentrations: 0.5, 5, and 20 mg/mL containing 2%, 5%, or 20% hydroxypropyl-beta-cyclodextrin, respectively. Liquid formulation was initially used to allow for maximum dose flexibility during early dose escalation. Serdemetan solution was used for doses up to 300 mg/d during once-daily dosing schedule and capsules were used for doses above 300 mg/d, for both once-daily and twice-daily dosing schedules. Immediate release, hard gelatin capsules of serdemetan were supplied in strengths of 10, 25, 100, and 200 mg. Medications metabolized by the CYP3A4, 2D6, 2C8, or 2C9 enzymes were used with caution. Drugs known to prolong the QT interval were prohibited.

### Safety evaluations

Safety assessments included monitoring for treatment-emergent adverse events (TEAE), DLTs, clinical laboratory tests (hematology, coagulation, blood chemistry, and urinalysis), vital signs, physical examinations, and carotid duplex ultrasound scan (preclinical studies had suggested carotid artery contraction as a potential toxicity). Electrocardiograms (ECG) were obtained at each specified clinic visit and analysis, and multiple gated acquisition scans were done at the conclusion of each cycle to monitor cardiac function while on study.

Adverse events were evaluated in accordance with National Cancer Institute Common Terminology Criteria, Version 3.0 (8) and were monitored up to 30 days after the last dose of study drug.

### Pharmacokinetic evaluations

**Blood and urine sample collection.** Venous blood samples (3 mL) were collected on days 1 and 21 at 0.5, 1, 2, 3, 4, 5, 6, 8 (or immediately before the second daily dose for twice-daily schedule), and 24 hours postdose, during cycle 1. Predose blood samples were collected within 15 minutes before dosing on days 1, 3, 7, 10, and 14 in cycle 1, and on day 21 of each subsequent cycle. Several blood sample collections were done immediately after ECG recordings. Urine samples were collected only during cycle 1, on days 1 and 21, within 30 minutes before dosing and for the intervals 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours.

Food effect and drug-drug interactions were also investigated as part of this study but will be reported separately.

**Bioanalytical procedures.** Plasma and urine concentrations of serdemetan were determined using a validated liquid chromatography–mass spectrometry method at the department of Bioanalysis, Johnson & Johnson Pharmaceutical Research & Development. The lower limit of quantification was 0.5 ng/mL.

### Pharmacodynamic evaluations

The study was designed to investigate parameters of serdemetan activity, based upon its shown ability to induce p53 (and based upon its originally proposed mechanism of action as an HDM2 inhibitor). These parameters included p53 and Ki67 levels detected via immunohistochemical staining and serum levels of macrophage inhibitory cytokine-1 (MIC-1) protein. Skin biopsies (at baseline and on day 21 of cycle 1) and tumor biopsies (on day 21 of cycle 1) were collected from patients expected to achieve serum  $C_{max}$  concentrations greater than 100 ng/mL and 195 ng/mL, respectively, for analysis of p53 and Ki67. Levels of MIC-1 were evaluated using ELISA of venous blood samples (5 mL), collected at baseline and on days 3, 10, and 21 in cycle 1, on day 21 in subsequent cycles, and at the end of treatment.

Immunohistochemistry (IHC) staining was done using standard technique. Antibodies used were p53 mouse monoclonal clone (clone DO-1; Santa Cruz Biotechnology) and Ki67 antigen mouse monoclonal clone (clone MIB-1, N1633; Dako). MIC-1 was evaluated using standard ELISA methods, in which we used the MIC-1 ab Ab26G6H6 for capture. For imaging and quantification, Ki67 and p53-stained slides of skin and tumor were imaged with a Mirax digital slide scanner (3DHitech) equipped with a 20× objective. The virtual images were observed with the Mirax Viewer software (3DHitech). Region of interest (ROI) of the epidermis or tumors were selected at a magnification of 40×. The selected ROI were saved as BMP files and further analysed with Axiovision image analysis software (version 4.6, Zeiss).

### Efficacy

Efficacy was evaluated by CT scan imaging after every 2 treatment cycles, with comparison to baseline scans. More frequent evaluation was allowed, if clinically indicated. The tumor assessments were done in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (9).

### Statistical analysis

The PK analysis set included patients who completed the PK assessments on day 1 of cycle 1. The safety analysis set included all patients who received at least 1 dose of serdemetan. Descriptive statistics was used to summarize safety and efficacy results.

The plasma concentration time curves were used to estimate  $C_{max}$ , time to reach maximum plasma concentration ( $t_{max}$ ), area under the concentration–time curve (AUC) from time 0 to 24 hours ( $AUC_{24h}$ ) for day 1 and 21, and in addition, the AUC from time 0 to infinity ( $AUC_{\infty}$ ) for day 1. For all evaluated doses, the effective half-lives ( $t_{1/2}$ ) were

estimated on the basis of the accumulation ratio between day 1 and 21. The relationship between plasma concentrations and QTcF (corrected QT using Fridericia's formula) values was evaluated on the basis of all data for which blood samples were taken immediately after ECG recording.

## Results

### Patient disposition and baseline characteristics

The majority (59.2%) of patients was male, most (98.6%) were white and 97.2% of patients had an ECOG performance status score of 0 or 1 at the time of study entry (Table 1). The most frequent tumor types were colorectal cancers, sarcomas, and melanomas.

Of the 71 enrolled patients, 62 were treated in the dose escalation phase (part 1): Fifty-one patients were on a once-daily dosing schedule, and 11 were on a twice-daily dosing schedule. Nine patients were treated in the expansion phase (part 2). A summary of the dose escalations and the observed DLT is provided in Table 2.

The median (range) number of administered cycles was 2 (1–21). Of the 71 enrolled patients, 14 patients (19.7%) received 1 treatment cycle, 33 (46.5%) received 2 cycles, 12 (16.9%) received 3 cycles, 4 (5.6%) received 4 or 5 cycles, and 8 (11.3%) received 6 or more cycles. Of the 14 patients

who did not receive 2 cycles, the reported reasons for discontinuation included disease progression (6), adverse event (5), and subject choice (3).

Forty-seven (66.2%) patients discontinued the study because of disease progression, 10 (14.1%) discontinued by their own choice, 9 (12.7%) discontinued after an adverse event, 3 (4.2%) discontinued because unsatisfactory therapeutic benefits, 1 (1.4%) discontinued because of new primary malignancy, and 1 (1.4%) discontinued because of close out of the trial.

### Safety

The first DLT observed during dose escalation occurred in the 300-mg daily cohort, when 1 patient of the first 4 treated (1 patient did not complete the first cycle of therapy) experienced a grade 3 QTc prolongation (Table 2). On subsequent expansion of this cohort with 3 additional patients failed to show any additional DLTs, dose escalation proceeded until the 400-mg daily dose was reached, at which time 2 of the 3 patients treated experienced DLTs. As a result, the 350-mg daily dose cohort was further expanded with 4 patients. Although there were no observed DLTs in any patient in this expansion cohort, 1 patient did require dose de-escalation. This fact, and concern over the potential of QTc prolongation toxicity, prompted further expansion of the 300-mg daily dose cohort with 9 additional patients, all of which were treated without any additional observed DLTs. Thus, with the absence of any observed DLTs at the 350-mg dose (Table 2), 350 mg daily was identified as the protocol-defined MTD.

In light of the observed QTc prolongation in the daily dosing schedule, a twice-daily dosing escalation was also done in the expectation that a lowered  $C_{max}$  might mitigate the risk of this toxicity. Two cohorts were treated on a twice-daily dosing schedule (150 and 200 mg), with the resulting observation of QTc prolongation as a DLT at both doses. The MTD for this dosing schedule was determined to be 150 mg twice daily, based upon the additional finding of a grade 3 rash in the 200-mg twice-daily cohort.

The DLTs observed during the study were grade 3 QTc prolongation ( $n = 4$ ), grade 3 rash and itching ( $n = 1$ ), and grade 3 tremor ( $n = 1$ ; Table 2). No grade 4 TEAEs were reported during the DLT period.

Most (98.6%) patients reported 1 or more TEAEs during the study. A summary of the most frequently observed (>10% incidence) TEAEs, and their frequency of grade 3 and 4 severity is provided in Table 3. The most frequently occurring grade 3 TEAEs reported as possibly related to the study drug were as follows: QTc prolongation [ $n = 6$  (8.5%)]; asthenia/fatigue [ $n = 9$  (12.7%)]; and diarrhea, decreased appetite, and abnormal hepatic function [each in 2 (2.8%) patients]. With the exception of QTc prolongation (discussed below), the presence of an exposure-related risk of these toxicities was difficult to determine, due to the small number of patients enrolled into the majority of dose cohorts (data not shown). Grade 4 TEAEs reported after the DLT period included asthenia, hypocalcemia, hypercalcemia, hypophosphatemia, spinal cord compression,

**Table 1.** Baseline demographic and clinical characteristics

Characteristic	All patients ( $n = 71$ )
Age (y), median (range)	57 (19.80)
Category, $n$ (%)	
>65	15 (21.1)
≤65	56 (78.9)
Gender, $n$ (%)	
Men	42 (59.2)
Women	29 (40.8)
Race, $n$ (%)	
Caucasian	70 (98.6)
Other <sup>a</sup>	1 (1.4)
ECOG <sup>b</sup> performance status, $n$ (%)	
0	20 (28.2)
1	49 (69.0)
2	2 (2.8)
Tumor type, $n$ (%)	
Colorectal	19 (26.8)
Sarcoma	12 (16.9)
Melanoma	8 (11.3)
Breast	7 (9.9)
Renal	3 (4.2)
Ovary	2 (2.8)
Pancreatic	2 (2.8)
Other	18 (25.4)

<sup>a</sup>One patient was described as "mixed race";

<sup>b</sup>Eastern Cooperative Oncology Group.



**Table 2.** Overview of dose escalation and DLTs

Dose cohort (mg)	Dosing schedule	Patients treated (n)	DLT (n)	DLT adverse event <sup>a</sup>
4	Daily	4	0	
8	Daily	3	0	
20	Daily	3	0	
40	Daily	4	0	
60	Daily	4	0	
90	Daily	4	0	
150	Daily	4	0	
225	Daily	7	0	
300	Daily	16 <sup>b</sup>	1	QTc prolongation
350	Daily	8 <sup>c</sup>	0	
400	Daily	3	2	Rash; QTc prolongation
150	Twice daily	8 <sup>d</sup>	1	QTc prolongation
200	Twice daily	3	2	Tremor; QTc prolongation

<sup>a</sup>All DLTs were of grade 3 severity.

<sup>b</sup>Includes 7 patients from original dose escalation and 9 patients from subsequent cohort expansion.

<sup>c</sup>Includes 4 patients from original dose escalation and 4 patients from subsequent cohort expansion.

<sup>d</sup>Includes 4 patients from original dose escalation and 4 patients from subsequent cohort expansion.

abnormal hepatic function, and dyspnea, of which only hypophosphatemia was reported as possibly related to the study drug. There seemed to be minimal, if any, effect on cardiac left ventricular function, as only 1 of the 72 study patients (dosed at 300 mg daily) exhibited a decrease in LVEF of 10% or more (a decrease from 82% at baseline to 57% at the end of cycle 2).

Laboratory chemistries were independently investigated for evidence of toxicity. Grade 4 toxicities were seen in 1 patient with hypocalcemia, 8 patients with gamma-glutamyltransferase (GGT) elevations, and 1 patient with hypophosphatemia. The abnormalities in serum GGT and alkaline phosphatase (ALP) levels were notable for both severity and frequency (grade 3 or 4 toxicities in more than 10% of patients). Serum GGT abnormalities of grade 3 and 4

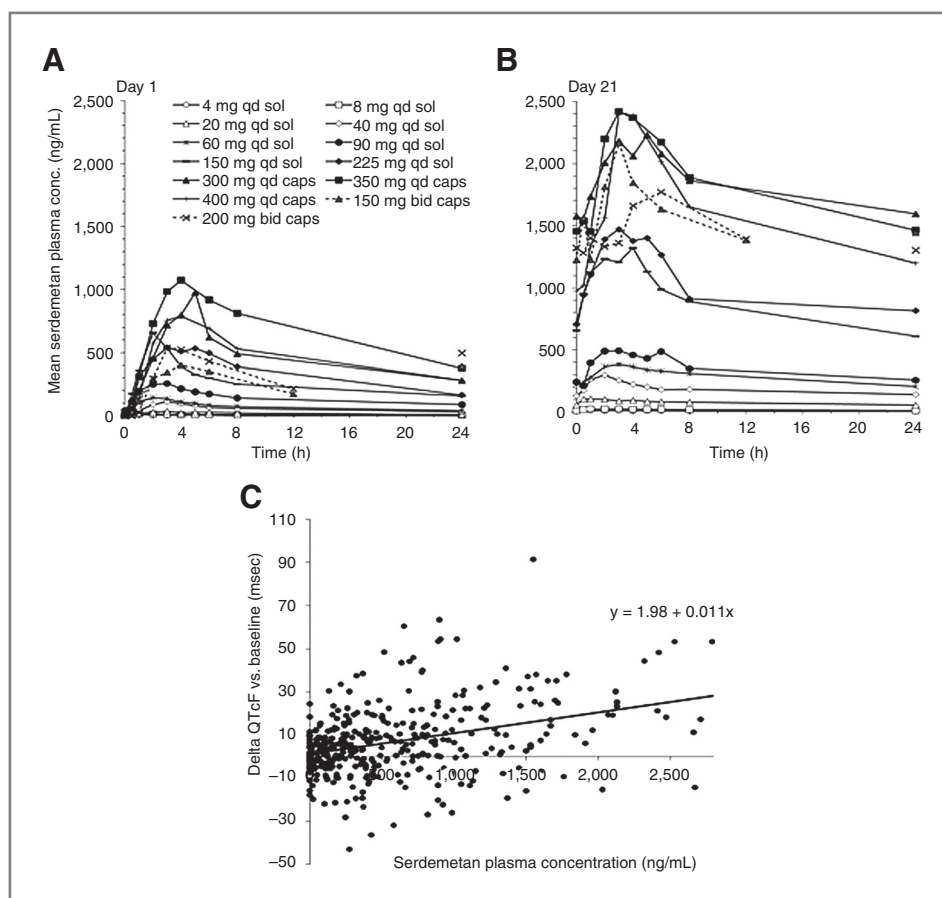
severity were reported in 26 patients [grade 3:  $n = 18$  (25.7%) and grade 4:  $n = 8$  (11.4%)], 24 of which had started the study with abnormally elevated GGT levels (toxicity  $\geq$  grade 2). ALP of grade 3 was seen in 7 (10%) patients, 2 of whom had no worsening from baseline. This level of toxicity, however, was not reflected in other indicators of hepatobiliary damage, including total bilirubin (grade 3:  $n = 1$ ; 1.4%), and the liver transaminases, alanine aminotransferase (grade 3:  $n = 4$ ; 5.7%) and aspartate aminotransferase (grade 3:  $n = 3$ ; 4.3%).

The predominant hematologic toxicity reported in this study was lymphopenia with 11 (16.4%) patients showing grade 3 toxicity and 3 (4.5%) patients showing grade 4 toxicity, with the majority (12) of these patients exhibiting worsening lymphocyte counts after initiation of serdemetan therapy. Other grade 3 hematologic toxicities were reported in only 2 (3%) patients: 1 patient experienced grade 3 anemia during the first cycle, after starting the study with anemia of grade 1, and the second patient experienced an episode of pancytopenia (grade 3 neutropenia, anemia, and leukopenia, and grade 2 thrombocytopenia), during the fifth treatment cycle. There were no instances of grade 4 toxicities observed in these hematologic parameters.

Twelve (16.9%) patients discontinued the study due to TEAEs, of which 6 discontinued because of TEAEs considered related to study drug [QTc prolongation ( $n = 4$ ); abnormal hepatic function ( $n = 1$ ); anemia and thrombocytopenia ( $n = 1$ )]. Ten (14.1%) patients experienced QTcF increases of more than 60 msec from baseline, of which 5 patients showed QTcF of more than 500 msec. The relatively frequent observation of QTc prolongation prompted a more thorough examination of this toxicity. Detailed analysis of observed QTc changes, as a function of corresponding plasma levels of serdemetan, suggested a positive correlation (Fig. 1C).

**Table 3.** TEAEs experienced by more than 10% of patients

TEAE	Total patients n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	47 (66.2)	1 (1.4)	0
Vomiting	34 (47.9)	1 (1.4)	0
Decreased appetite	21 (29.6)	4 (5.6)	0
Asthenia/fatigue	28 (39.4)	9 (12.7)	1 (1.4)
Constipation	16 (22.5)	1 (1.4)	0
Insomnia	16 (22.5)	0	0
QTc prolongation	11 (15.5)	6 (8.5)	0
Abnormal hepatic function	10 (14.1)	4 (5.6)	1 (1.4)
Anemia	9 (12.7)	1 (1.4)	0



**Figure 1.** Plasma concentration–time profile of serdemetan. A, plasma concentration–time profile of serdemetan in 4 to 400 mg dose group on day 1; bid, twice daily; sol, serdemetan solution; cap, serdemetan immediate release capsules. B, plasma concentration–time profile of serdemetan in 4 to 400 mg dose group on day 21; bid, twice daily; sol, serdemetan solution; cap, serdemetan immediate release capsules. C, correlation of serdemetan plasma levels with QTcF changes. Plasma levels of serdemetan were assessed on the day 21 visit of cycle 1 and immediately after ECGs were done. Plasma levels were correlated to changes in QTcF, as determined by comparing the QTcF interval in the time-matched ECG to that on pretreatment ECG. The resulting graph shows a positive correlation, suggesting a dose-dependent effect on the QTcF interval.

Eight (11.3%) patients died during the study due to general physical health deterioration ( $n = 3$ ), CNS metastases ( $n = 1$ ), lung infection and pyrexia ( $n = 1$ ), dyspnea ( $n = 1$ ), pneumonia ( $n = 1$ ), or intestinal obstruction ( $n = 1$ ). All deaths were considered either not related, or unlikely related, to study drug by the investigators.

### Pharmacokinetics

Serdemetan was rapidly absorbed after oral administration, with  $C_{max}$  generally observed 2 to 3 hours after administration of the solution and 3 to 4 hours after administration of capsules (Supplementary Table S1, Fig. 1A and B). At 24 hours after once-daily dosing, levels were less than half of their peak values. Plasma concentrations reached steady state after 10 days of dosing, with no further accumulation observed through day 21. After a single dose and at steady state, serdemetan exposure as expressed by  $C_{max}$  and AUCs increased dose proportionally. At steady state,  $C_{max}$  and  $AUC_{0-24h}$  were 3 to 4 times higher than after single dose, indicating an effective  $t_{1/2}$  in the order of 2 to 3 days. The mean steady-state  $C_{max}$  was 2,330 ng/mL after 300-mg once-daily dosing and slightly lower after 150-mg twice-daily dosing. Overall, interpatient variability (CV%) was low (<50%) for all exposure parameters for both dosing schedules. Less than 10% of the daily dose of serdemetan

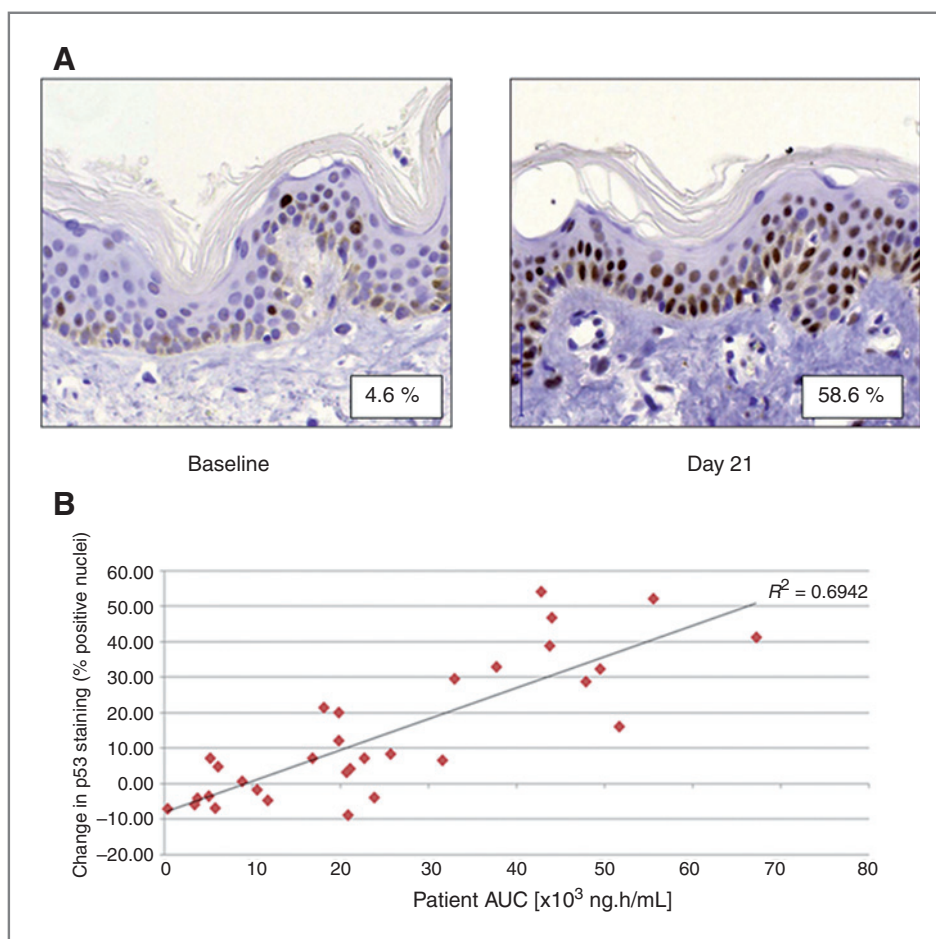
was recovered as parent drug in urine. The mean renal clearance was 1 L/h.

Changes in QTcF were directly related to serdemetan plasma concentrations (Fig. 1C). Steady-state  $C_{max}$  concentrations after 300-mg once-daily dosing caused QTcF changes of more than 25 msec on average.

### Pharmacodynamics

Biomarker studies provided evidence of serdemetan activity in both surrogate and tumor biopsy tissue. The p53 levels in skin biopsies increased on day 21, compared with day 1. The increase was exposure related (Fig. 2), with higher levels of nuclear p53 staining observed in skin biopsies taken from patients with higher AUC exposures. Conversely, Ki67 levels in skin biopsies decreased from day 1 to 21, but this was observed at the 300 mg/d dose only. Evidence of response in tumors was less robust. Significant increases in p53 expression were only observed in 8 patients of 13, from whom the tumor biopsies were collected. No significant changes in Ki67 levels were observed relative to baseline in these tumor specimens. A dose-dependent increase in serum MIC-1 levels was measured as a potential PD marker of serdemetan-induced p53 activation. Serdemetan treatment reliably resulted in increase of MIC-1 serum levels at day 21 compared with baseline, however

**Figure 2.** p53 measurement in skin tissue of patients. A, IHC staining of p53 (brown) of skin from patients receiving serdemetan at day 1 (left) or day 21 (right). Insert indicates the quantification of the p53 signal (mean percentage of positive nuclei). B, graph showing correlation of drug exposure to change in p53 from baseline in skin of patients treated with serdemetan. The correlation has a  $R^2$  value of 0.6942.



the magnitude of the effect was not observed to be dose dependent.

### Efficacy

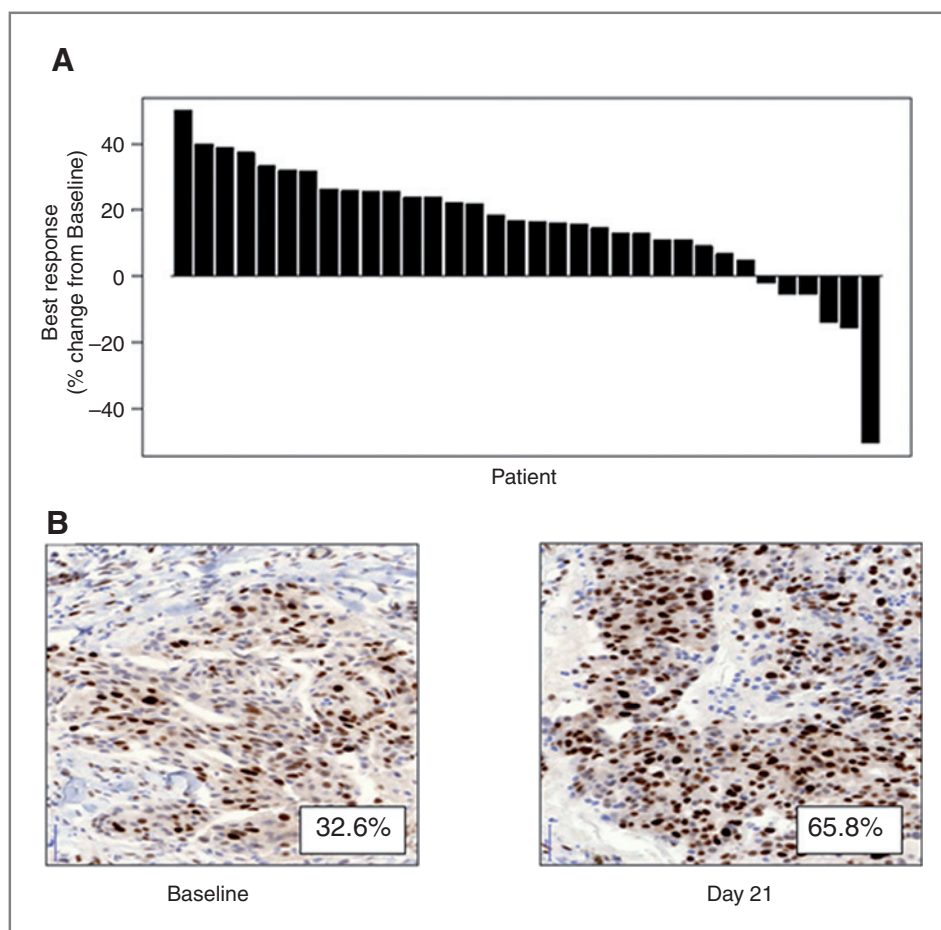
Of the 71 patients treated in this study, 57 were evaluable for efficacy, having had both a baseline and at least 1 post-treatment study done for comparison. Of the 14 nonevaluable patients, 6 were reported to have discontinued as a result of an adverse event, 6 as a result of disease progression, and 2 by patient choice. One patient with breast cancer, receiving serdemetan 150 mg twice daily, showed a partial response (this patient also reported 102% increase in p53 levels in tumor biopsies; Fig. 3B). Seven additional patients exhibited a decrease in tumor size but did not meet criteria for partial response. Twenty-two (38.6%) patients had stable disease as their best overall response (evaluated as per RECIST guideline), with 4 of these patients exhibiting prolonged stable disease with extended courses of serdemetan therapy (of 126, 196, 308, and 420 days in patients with angiosarcoma, breast cancer, Hurthle cell carcinoma, and ependymoma, respectively). Thirty-four (59.6%) patients had progressive disease as their best overall response. The maximum tumor reduction in all patients receiving doses above 150 mg/d, the threshold that resulted in p53 induction in skin biopsies, is shown in Figure 3A.

### Discussion

Serdemetan is a novel tryptamine derivative that was originally isolated in a chemical screen, on the basis of its ability to induce p53 expression. Initial preclinical studies suggested that its mechanism of action included the inhibition of HDM2, but continued investigations, conducted in parallel with this trial, recently disproved this hypothesis by showing that serdemetan was similarly active in cell lines and xenografts lacking p53 function, or in HDM2-deficient experimental models. Although its exact mechanism of action remains under investigation, its ability to induce S-phase arrest and apoptosis in a wide range of tumor models, independent of p53 status, has been repeatedly shown.

This first-in-human study of serdemetan evaluated incremental doses of serdemetan to identify the DLTs and the MTDs, for both once-daily and twice-daily dosing schedules. Safety, PK, and PD (using biomarker studies) profiles of serdemetan were characterized; efficacy data for antitumor activity was also collected.

Serdemetan was rapidly absorbed after oral administration when given as a solution or capsule. Capsules showed a lag time of 0.5 to 1 hour, followed by rapid absorption that was similar to absorption from the solution. Steady-state



**Figure 3.** Clinical responses to serdemetan in patients and tumors. A, waterfall plot showing the best tumor responses in all patients who received daily doses of 150 mg or greater. B, p53 IHC staining in tumor samples from patient exhibiting confirmed partial response. Left panel shows baseline p53 staining (brown). Right panel shows p53 staining (brown) from the same patient on day 21 of cycle 1. The respective levels of p53 induction are indicated (mean percentage of positive nuclei).

exposure was achieved within 10 days of daily administration of serdemetan. The elimination of serdemetan was slower than anticipated, as indicated by the overall effective  $t_{1/2}$  of 2 to 3 days, in contrast to preclinical studies, in which the elimination  $t_{1/2}$  was 3 to 8 hours in rats, mice, and dogs (data not shown).

The MTD of serdemetan was found to be 350 mg for once-daily schedule and 150 mg for twice-daily schedule. The main DLT reported was grade 3 QTc prolongation (observed in 4 patients). Grade 2 QTc prolongation was observed in 10 additional patients, identifying QTc prolongation as the primary safety concern associated with serdemetan therapy. QTc prolongation was directly correlated with serdemetan plasma concentration. The other DLTs included rash, pruritis, and tremor. Although 8 deaths occurred during the study, all were considered to be unlikely related to serdemetan therapy by the study investigator.

Lymphopenia was observed in the majority of patients and more than 20% patients experienced grade 3 or 4 severity. The TEAEs of anemia, thrombocytopenia, and neutropenia were minimal, indicating that serdemetan has little effect on bone marrow, and, therefore, might be used in combination with existing cytotoxic chemotherapies. Although more than 30% patients experienced grade 3 or 4 elevations in GGT, the majority of these patients had

elevated GGT levels at baseline, suggesting that true incidence rate for this toxicity may be lower than that was observed. Although the MTD was determined to be 350 mg daily, as defined by the protocol, the next lower dose of 300 mg daily was recommended for subsequent phase II studies, in light of the observed dose-dependent nature of the QTc prolongation (Fig. 1C), and the similar PK profiles of the 350 mg and 300 mg doses observed in this study (Fig. 1B).

Biomarker analyses done before and after the serdemetan therapy showed dose-dependent increase in p53 levels in skin biopsies, from doses 150 mg/d onwards. Although the number of samples available for tumor biomarker analysis was limited, a trend toward p53 induction in tumors was observed. Thus, the observation of serdemetan-induced p53 expression in human tumors in this study is consistent with preclinical studies showing similar activity in both cell lines and xenograft models. Serum levels of MIC-1, a marker of p53 activation, were seen to rise after treatment with serdemetan, however, the increase was not dose dependent, and therefore MIC-1 levels were considered to be a poor pharmacodynamic marker for serdemetan.

Serdemetan showed a modest clinical activity based on the results of antitumor assessment, with 1 patient with advanced breast cancer exhibiting a partial response. Interestingly, a 102% increase in p53 staining was observed in



the tumor of this patient. The disease remained stable in approximately 40% of patients. Some of these patients with stable disease received extended courses of serdemetan therapy, at doses that reliably induced p53 in skin biopsies. These findings, in addition to the other observed minor responses, suggest a direct effect of serdemetan on at least a subset of tumors.

In summary, this first-in-human study identified the MTD of serdemetan in patients with solid tumors in advanced stage or refractory to available therapy. Although serdemetan showed evidence of clinical efficacy in this patient population with limited treatment options, the identification of exposure-related QTc toxicity is of concern. The development of serdemetan derivatives lacking this liability is currently under consideration.

### Disclosure of Potential Conflicts of Interest

L. van Beijsterveldt was an employee of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. at the time of the study. S. Platero, R. Knoblauch, S.H. Zhuang, Z. Yuan, and B. Hall are employees of Johnson & Johnson Pharmaceutical Research & Development, L.L.C. J. Taberner, P. Schöffski, J. Capdevila, L. Dirix, J.A. Lopez-Martin, and A. Cervantes have no conflict of interest. All authors met ICMJE criteria and all those who fulfilled

those criteria are listed as authors. All approved submission to this journal. The sponsor provided a formal review of the manuscript.

### Acknowledgments

We thank Silvija Kraljevic for assistance with protocol development and trial coordination; Ms. Caroline Lannie for assistance in pharmacokinetic and pharmacodynamic analysis; Dr. Tine Casneuf and Ms. Ilse Goris for assistance in biomarker analysis; Dr. Lutgart de Bie for efficient trial coordination and operations; and Dr. Namit Ghildyal for editorial support (all from Johnson & Johnson Pharmaceutical Research & Development). Dr. Sarika Shirke (SIRO Clinpharm Pvt. Ltd.) provided writing assistance; funding provided by Johnson & Johnson Pharmaceutical Research & Development. We also thank the study participants and their families, without whom this study would never have been accomplished.

### Grant Support

The work was funded by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, N.J.

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Received April 27, 2011; revised July 1, 2011; accepted July 26, 2011; published OnlineFirst August 10, 2011.

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