Citation: Clin Transl Sci (2019) 12, 291–301; doi:10.1111/cts.12618

ARTICLE

Safety, Pharmacokinetics, and Pharmacodynamics of ASP3662, a Novel 11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor, in Healthy Young and Elderly Subjects

Susan Bellaire[1], Mark Walzer[2,*], Tianli Wang[3], Walter Krauwinkel[4], Nancy Yuan[3] and Gerard J. Marek[5]

Inhibition of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) represents a potential mechanism for improving pain conditions. ASP3662 is a potent and selective inhibitor of 11β-HSD1. Two phase I clinical studies were conducted to assess the safety, tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) of single and multiple ascending doses of ASP3662 in healthy young and elderly non-Japanese and young Japanese subjects. Nonlinear, more than dose-proportional PKs were observed for ASP3662 after single-dose administration, particularly at lower doses (≤ 6 mg); the PKs at steady state were dose proportional, although the time to ASP3662 steady state was dose dependent at lower doses (≤ 2 mg). Similar PKs were observed among young Japanese, young non-Japanese, and elderly non-Japanese subjects. Specific inhibition of 11β-HSD1 occurred after both single and multiple doses of ASP3662. A marked dissociation between PKs and PDs was observed after single but not multiple doses of ASP3662. ASP3662 was generally safe and well tolerated.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) modulates the conversion of inactive cortisone to active cortisol and has been implicated in pathways related to pain conditions.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Two phase I clinical studies assessed the safety, tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) of single and multiple ascending doses of ASP3662, a novel, specific 11β-HSD1 inhibitor, in healthy young and elderly non-Japanese and young Japanese subjects.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Nonlinear PKs were observed following administration of a single dose of ASP3662 in the lower dose range, whereas steady-state ASP3662 PKs were dose proportional across the entire dose range. No significant differences in ASP3662 PKs were observed between the different populations. Specific inhibition of 11β-HSD1 occurred after both single and multiple doses of ASP3662; however, there was a dissociation between the single-dose PKs and the peripheral PD effects.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These studies provide information on the PKs and PDs of ASP3662 and determined the dose range to achieve full inhibition of 11β-HSD1 after multiple doses. These data will be valuable in future studies of the clinical utility of this mechanism.

The 11β-hydroxysteroid dehydrogenases (11β-HSDs) are enzymes that regulate the intracellular levels of glucocorticoids. The 11β-HSD enzymes consist of two isoforms: the nicotinamide–adenine dinucleotide phosphate reduced-dependent type 1 (11β-HSD1) converts inactive cortisone to active cortisol, and the nicotinamide–adenine dinucleotide-dependent oxidative type 2 (11β-HSD2) converts cortisol to cortisone. The 11β-HSD1 enzyme is abundantly expressed and colocalized with the glucocorticoid receptor in multiple tissues, including liver, lungs, fat, and the central nervous system where it plays an integral role in modulating cortisol's effects throughout the body.[1,2] The 11β-HSD2 enzyme is expressed in tissues containing mineralocorticoid receptors, such as the kidneys and placenta, and plays a protective role by preventing activation of mineralocorticoid receptors by endogenous glucocorticoids.[3]

ASP3662 is a novel small molecule agent developed by Astellas Pharma that is a potent and selective inhibitor of 11β-HSD1. ASP3662 has high affinity (K_i 5.3 nM) and competitive binding for human 11β-HSD1 and demonstrates no inhibition of 11β-HSD2 at concentrations < 3,000 nM (Internal study reports 3662-PH-0001 and 3662-PH-0001-0004).

[1]Formerly with Astellas Pharma Europe BV, Leiden, The Netherlands; [2]Astellas Pharma Global Development, Northbrook, Illinois, USA; [3]Formerly with Astellas Pharma, Inc., Northbrook, Illinois, USA; [4]Astellas Pharma, Inc., Leiden, The Netherlands; [5]Astellas Pharma, Inc., Northbrook, Illinois, USA. *Correspondence: Mark Walzer (Mark.Walzer@astellas.com)

Received: August 27, 2018; accepted: December 31, 2018. doi:10.1111/cts.12618

Preclinical studies in rats have shown that ASP3662 has significant analgesic effects in a number of models of neuropathic and dysfunctional pain.[4] Furthermore, conditions characterized by altered glucocorticoid homeostasis, such as agitation associated with Alzheimer's disease, may also benefit from this mechanism.[5,6] To date, several selective and nonselective 11β-HSD1 inhibitors have been developed for indications such as type 2 diabetes mellitus and metabolic syndrome (e.g., RO5093151, RO5027383, MK-0916, and INCB13739),[7–9] nonalcoholic fatty liver disease (e.g., RO5093151),[10] hypertension, and obesity (e.g., MK-0736 and AMG 221),[11,12] and Alzheimer's disease (ABT-384),[13] with limited success in part due to modest efficacy when compared with standard of care.

Two phase I clinical studies assessed the safety, pharmacokinetics (PKs), and pharmacologic effects of ASP3662 in healthy young and elderly non-Japanese and young Japanese subjects. Results from single ascending dose (SAD) and multiple ascending dose (MAD) studies for a molecule previously evaluated in a novel indication, painful diabetic peripheral neuropathy (NCT02372578), are reported herein.

METHODS

These studies were conducted in accordance with the study protocols, Good Clinical Practice and International Conference on Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles of the Declaration of Helsinki. All subjects provided written informed consent and a Health Insurance Portability and Accountability Act authorization form. The study protocols have undergone approval via Independent Ethics Committees.

Study population

Subjects enrolled in the SAD study were healthy young male or female adults aged 18–55 years with a body mass index (BMI) of 18.5–30 kg/m^2. Subjects enrolled in the MAD study were (i) healthy young adult first-generation Japanese subjects aged 20–55 years who maintained a Japanese lifestyle, including diet, and with a BMI of 17.6–26.4 kg/m^2; and (ii) healthy non-Japanese subjects aged 18–55 years (young adult) or ≥ 65 years (elderly), of non-Asian descent with a BMI of 18.5–32 kg/m^2. Subjects were excluded from part 2 of the MAD study if they had used any licorice or licorice-flavored products containing glycyrrhetinic acid within 7 days before enrollment.

Study design

The SAD study was a first-in-human, randomized, double-blind, placebo (PBO)-controlled, parallel-group study conducted at one contract site in the United States. Following a 21-day screening period, subjects were admitted to the study center on day –1 and randomized to one of six ASP3662 dose cohorts: 1, 3, 6, 10, 30, or 60 mg. In each cohort, six subjects were randomized to ASP3662 and two were randomized to PBO. Subjects received a single oral dose of ASP3662 or PBO on day 1 under fasting conditions and remained in the study center for PK and pharmacodynamic (PD) evaluations through day 4. Dose escalation was limited by an exposure limit (1,952 ng/mL for maximum plasma concentration (C_{max}) and 23,110 for area under the concentration–time curve (AUC)), defined as 1/10 of the maximum tolerated dose observed in dogs, which was associated with vomiting and was approximately threefold to fourfold higher than the no observed adverse effect level in dogs (Internal study report 3662-TX-0016).

The MAD study was a randomized, PBO-controlled, subject-blinded and investigator-blinded, parallel-group study conducted in two parts at two contracted study centers in the United States. This study utilized healthy volunteers instead of patients to understand the safety, tolerability, and PD effects of ASP3662 on the hypothalamic-pituitary-adrenal (HPA) axis independent of a potential interaction with a disease state. Part 1 investigated three doses (10, 20, and 50 mg) of ASP3662 in healthy young adult Japanese and non-Japanese subjects, and healthy elderly non-Japanese subjects. Following a 28-day screening period, subjects were admitted to the clinic on day –2. Urine endocrine markers were collected on day –1. Young Japanese subjects were randomized to PBO or ASP3662 10, 20, or 50 mg, and young non-Japanese subjects were randomized to PBO or ASP3662 20 or 50 mg. In each cohort, eight subjects were randomized to ASP3662 and two were randomized to PBO. Twelve elderly non-Japanese subjects were randomized to ASP3662 20 mg (n = 9) or PBO (n = 3). Subjects received a single dose of PBO or ASP3662 on day 1, followed by a 4-day washout period and then q.d. doses of PBO or ASP3662 for 14 days (days 5–18). Subjects remained in the clinic for two additional days (days 19–20) for safety and PK sample collection. Part 2 was an open-label, nonrandomized study to characterize the PKs of ASP3662 at lower doses (0.2, 0.4, 0.7, and 2 mg) in healthy young non-Japanese subjects. Following a 28-day screening period, subjects were admitted to the clinic on day –2. Baseline samples for urine endocrine markers were collected on day –1. The first two cohorts were designed to collect PK data after both single and multiple dosing of ASP3662 0.7 or 2 mg. Subjects received a single dose of ASP3662 on day 1, followed by a 6-day washout period and q.d. doses of ASP3662 for 14 days (days 7–20). Subjects remained in the clinic for an additional day (day 21) for safety and PK sample collection. Outpatient visits and a follow-up visit for PK and PD sample collection and safety assessments occurred on days 22–27 and on day 34. Subjects in two additional cohorts received ASP3662 0.2 or 0.4 mg. Subjects in the 0.4 mg cohort received ASP3662 once daily for 14 days (day 1–14), and subjects in the 0.2 mg cohort received a loading dose of 3 mg ASP3662 on day 1 followed by q.d. doses of 0.2 mg on days 2–14. Subjects remained in the clinic for an additional day for safety and PK sample collection and were discharged on day 15. Outpatient visits and a follow-up visit for PK and PD sample collection and safety assessments occurred on days 16–21 and on day 28.

Study drug administration

ASP3662 was provided as 0.1, 1, or 10 mg tablets. All doses of ASP3662 were taken with 240 mL water at room temperature. On the study days in which PK samples were collected at multiple timepoints, ASP3662 or PBO were administered

after a 10-hour fast, and food was not allowed for 4 hours after drug administration. In the MAD study, on the days in which no PK samples or only trough samples were collected, ASP3662 was administered once daily at approximately the same time, and breakfast was allowed after dosing.

Dose rationale

Based on available *in vivo* pharmacology data, the minimal pharmacological active oral dose was determined to be 0.03 mg/kg in mice, which provided a human equivalent dose of 0.15 mg. Based on 4-week toxicology data in the most sensitive species (rat), the maximum recommended starting dose derived from the no observed adverse effect level was 10 mg. Given the large difference in starting dose between these two approaches, a starting dose of 1 mg was selected, which, based on monkey positron emission tomography (PET) data, was predicted to induce 30–50% inhibition of 11β-HSD1 in the brain. Moreover, as other 11β-HSD1 inhibitors have previously been clinically evaluated and shown to be safe and well tolerated, a more conservative starting dose was not selected. Given the observed differences in sensitivity among species, the desired target exposure and enzyme occupancy in humans for the different intended indications was not clearly defined. Therefore, the initial SAD/MAD studies were designed to evaluate doses anticipated to achieve maximal target inhibition of 11β-HSD1 and to provide safety, tolerability, and PK data at exposures several fold above the estimated therapeutic range. A human PET study was included in the early clinical development plan, and data from this study were also used for selecting the dose range.

The starting dose of 10 mg ASP3662 used in part 1 of the MAD study was chosen because it was considered safe based on the evaluation of data from the SAD study. The highest dose of ASP3662 50 mg was selected after prediction models based on the PK data from the SAD study and the 10-mg and 20-mg cohorts showed a < 5% risk of exceeding the exposure limit. Dose-escalation decisions were based on PK, safety, and tolerability data. The clinical PD data indicating that full inhibition of peripheral 11β-HSD1 was achieved with 3 mg ASP3662 were not available at the time of dose escalation.

Study assessments and sample collection

Plasma PK assessments following a single dose of ASP3662 included AUC from predose extrapolated to infinity (AUC_{inf}), C_{max}, terminal elimination half-life ($t_{½}$), total oral clearance (CL/F), and time of maximum plasma concentration (T_{max}). Plasma PK assessments for multiple dose ASP3662 included AUC for a dosing interval (AUC_{tau}), C_{max}, trough concentration (C_{trough}), $t_{½}$, T_{max}, CL/F, and accumulation ratio based on AUC (R_{ac} (AUC)). During the SAD study, serial blood samples for the analysis of plasma PK parameters were collected from predose to 72 hours after study drug administration. For the 6-mg, 30-mg, and 60-mg ASP3662 cohorts, additional blood samples were collected 96 and 120 hours after study drug administration. Urine samples for analysis of PKs and PDs (i.e., cortisol, cortisone, tetrahydrocortisol (5α and 5β), and tetrahydrocortisone) were collected from predose to 72 hours after study drug administration. Plasma and urine concentrations of ASP3662 were measured using a validated high-performance liquid chromatography with tandem mass spectrometry method.

Exploratory PD assessments included 11β-HSD1 activity (ratio of the tetrahydrometabolites of cortisol/cortisone in the urine), 11β-HSD2 activity (urine cortisol/cortisone ratio), 24-hour glucocorticoid (cortisol + cortisone + tetrahydrocortisol (5α + 5β) + tetrahydrocortisone), adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEA-s), and the cumulative amount of cortisol and cortisone excreted into urine from time of dosing to 24 hours postdose (A_e24), from 24–48 hours postdose (A_e24–48), and from 48–72 hours postdose (A_e48–72). Among all PD assessments, 11β-HSD1 activity is the most important, as this represents direct target inhibition, whereas the other PD parameters relate to the HPA axis and result in upstream and/or downstream effects (including homeostatic feedback loops) of 11β-HSD1 inhibition.

Safety was assessed in both studies through the reporting of the nature, frequency, severity, time of onset/offset, and relatedness to study drug of treatment-emergent adverse events (TEAEs), clinical laboratory evaluations (i.e., hematology, serum chemistry, and urinalysis), physical examination, including vital signs, and electrocardiograms, and central nervous system scales (Bond and Lader visual analogue scales, Addiction Center Inventory Short Form-49, and Profile of Moods States).

Statistical methodology

Formal sample size calculations were not performed. The sample size was based on previous experience, which was deemed sufficient to meet the objectives. To evaluate potential differences in PK due to age and ethnicity in the high-dose cohorts, given the observed coefficient of variance for C_{max} and AUC with a range of 25–50%, a sample size of eight subjects in each cohort would have at least 80% power to detect at least a twofold change in geometric means of ASP3662 exposure, using a two-group *t*-test with a 10% two-sided significance level.

Descriptive statistics were used to summarize baseline and demographic data, urine exploratory PD parameters, PK parameters, and all safety and tolerability data. TEAEs were coded using the Medical Dictionary for Regulatory Activities and summarized by system organ class. Plasma PK parameters were calculated using Phoenix version 6.3 (Certara, St. Louis, MO); urine PK parameters were calculated using SAS version 9.3 (Cary, NC). Plasma concentrations below the limit of quantification were assigned as zero during the calculations.

Dose-proportionality for AUC from predose (time 0) to the time of the last quantifiable concentration (AUC_{last}), AUC_{inf}, and C_{max} were analyzed separately using a power model, with regression of the dose-normalized natural log-transformed AUC_{last}, AUC_{inf}, and C_{max} on log-transformed ASP3662 dose to obtain 95% confidence interval for the slope.

RESULTS

Subject disposition

SAD study. Forty-eight subjects were randomized to receive PBO (*n* = 12) or ASP3662 (*n* = 36; **Table 1**). All 48 subjects (100%) were included in the safety analysis set

Table 1 Demographics and baseline characteristics (SAD study)

	PBO (*n* = 12)	ASP3662 1 mg (*n* = 6)	ASP3662 3 mg (*n* = 6)	ASP3662 6 mg (*n* = 6)	ASP3662 10 mg (*n* = 6)	ASP3662 30 mg (*n* = 6)	ASP3662 60 mg (*n* = 6)
Sex, *n* (%)							
Male	10 (83.3)	5 (83.3)	6 (100)	6 (100)	6 (100)	4 (66.7)	5 (83.3)
Ethnicity, *n* (%)							
Hispanic/Latino	3 (25.0)	0	2 (33.3)	3 (50.0)	1 (16.7)	0	3 (50.0)
Not Hispanic/ Latino	9 (75.0)	6 (100.0)	4 (66.7)	3 (50.0)	5 (83.3)	6 (100)	3 (50.0)
Race, *n* (%)							
White	5 (41.7)	4 (66.7)	3 (50.0)	4 (66.7)	5 (83.3)	3 (50.0)	5 (83.3)
African American	7 (58.3)	1 (16.7)	2 (33.3)	1 (16.7)	0	3 (50.0)	0
Asian	0	1 (16.7)	1 (16.7)	0	1 (16.7)	0	1 (16.7)
Other	0	0	0	1 (16.7)	0	0	0
Age, years							
Mean (SD)	37.4 (9.4)	44.0 (9.2)	32.2 (10.7)	36.2 (12.2)	34.3 (8.6)	34.8 (15.0)	31.2 (5.8)
Median	33.5	47.0	31.5	31.0	33.0	27.0	32.5
Height (cm)							
Mean (SD)	176.6 (9.0)	172.5 (7.3)	173.5 (9.9)	176.5 (5.8)	176.5 (6.6)	170.8 (8.4)	170.5 (11.0)
Median	177.6	174.7	172.2	174.7	175.3	172.5	171.5
Weight (kg)							
Mean (SD)	76.18 (13.31)	76.50 (14.10)	74.93 (8.80)	80.82 (5.29)	76.60 (10.00)	70.03 (6.85)	72.67 (7.55)
Median	75.80	79.90	74.60	78.95	78.00	68.10	75.30
BMI (kg/m^2)							
Mean (SD)	24.31 (2.90)	25.65 (4.04)	24.90 (2.19)	25.98 (2.21)	24.63 (3.34)	24.02 (2.05)	25.12 (3.01)
Median	24.10	26.20	24.20	26.05	25.20	23.95	25.15

BMI, body mass index; PBO, placebo; SAD, single ascending dose.

(SAF), and all 36 subjects (100%) randomized to ASP3662 were included in the PK analysis set (PKAS).

MAD study. *Part 1*. Sixty-two subjects were randomized to receive PBO (*n* = 13) or ASP3662 (*n* = 49; **Table 2**). All 30 (100%) young Japanese subjects were included in the SAF and in the PD analysis set (PDAS); 24 (100%) who were randomized to ASP3662 were included in the PKAS. Of 20 young non-Japanese subjects randomized to PBO (*n* = 4) or ASP3662 (*n* = 16), 2 withdrew consent and discontinued the study for reasons not related to the study drug: 1 randomized to receive PBO withdrew on day 17, and 1 randomized to 50 mg ASP3662 withdrew consent after receiving a single dose and q.d. doses on days 5–8. All 20 subjects were included in the SAF and PDAS, and all 16 subjects (100%) randomized to ASP3662 were included in the PKAS. All 12 elderly non-Japanese subjects randomized to PBO (*n* = 3) or ASP3662 20 mg (*n* = 9) were included in the SAF and PDAS; all nine subjects randomized to ASP3662 20 mg were included in the PKAS.

Part 2. Part 2 was designed and conducted to understand the effects of ASP3662 on 11β-HSD1 activity and other HPA axis parameters at doses lower than those shown in part 1 to completely inhibit 11β-HSD1. This decision was based on the availability of human PET data (data not shown). Twenty young non-Japanese subjects were enrolled in part 2 of the study and received ASP3662 (2 mg, *n* = 6; 0.7 mg, *n* = 6; 0.4 mg, *n* = 4; or 0.2 mg, *n* = 4; **Table 2**). All subjects except for two completed the study per the protocol. One subject in the ASP3662 2-mg group did not receive the last dose on day 20, and one subject in the ASP3662 0.2-mg group was lost to follow-up after receiving all the scheduled doses. All 20 subjects (100%) were included in the SAF, PDAS, and PKAS.

Plasma PK results

ASP3662 single-dose PKs from the SAD study. The mean plasma concentration–time profiles and plasma PK parameters of ASP3662 after single doses are reported in **Figure S1 and Table 3**, respectively. ASP3662 was rapidly absorbed, and C_{max} occurred with median T_{max} of 1.75–3.50 hours. Following C_{max}, plasma concentrations rapidly declined, and at ~ 24 hours postdose, a second peak or plateau was observed, which may indicate enterohepatic circulation. Overall, the single-dose PKs of ASP3662 were nonlinear with more than dose-proportional increases in both C_{max} and AUC parameters, particularly with lower doses (1–6 mg) where the variance was also high. The mean CL/F and mean apparent $t_{½}$ decreased with increasing dose. The derived PK from the 1-mg cohort should be interpreted with caution because most measurements were below the lower limit of quantification.

ASP3662 single- and multiple-dose PKs from the MAD study. The mean plasma concentration–time profiles of ASP3662 and its major nonactive metabolite, AS2570469,

Table 2 Demographics and baseline characteristics (MAD study)

	Part 1 – high dose						Part 2 – low dose			
	Young Japanese		Young non-Japanese		Elderly non-Japanese		Young non-Japanese		Young non-Japanese	
	PBO (*n* = 6)	ASP3662 (*n* = 24)	PBO (*n* = 4)	ASP3662 (*n* = 16)	PBO (*n* = 3)	ASP3662 (*n* = 9)	0.7 mg (*n* = 6)	2 mg (*n* = 6)	0.2 mg (*n* = 4)	0.4 mg (*n* = 4)
Sex, *n* (%)										
Male	4 (66.7)	17 (70.8)	3 (75.0)	7 (43.8)	1 (33.3)	4 (44.4)	3 (50.0)	3 (50.0)	2 (50.0)	2 (50.0)
Ethnicity, *n* (%)										
Hispanic/Latino	0	0	1 (25.0)	5 (31.3)	3 (100)	6 (66.7)	1 (16.7)	0	0	2 (50.0)
Not Hispanic/ Latino	6 (100)	24 (100)	3 (75.0)	11 (68.8)	0	3 (33.3)	5 (83.3)	6 (100)	4 (100)	2 (50.0)
Race, *n* (%)										
White	0	0	2 (50.0)	10 (62.5)	3 (100)	8 (88.9)	4 (66.7)	3 (50.0)	1 (25.0)	2 (50.0)
African American	0	0	2 (50.0)	4 (25.0)	0	1 (11.1)	2 (33.3)	3 (50.0)	3 (75.0)	2 (50.0)
Asian	6 (100)	24 (100)	0	0	0	0	0	0	0	0
Other	0	0	0	2 (12.5)	0	0	0	0	0	0
Age, years										
Mean (SD)	36.0 (10.7)	38.4 (9.8)	30.0 (4.5)	36.0 (10.3)	74.7 (5.9)	71.1 (6.9)	33.7 (9.5)	34.7 (6.3)	32.5 (11.2)	39.5 (10.4)
Median	33.5	39.0	29.0	32.0	77.0	69.0	31.0	34.0	31.0	36.0
Height (cm)										
Mean (SD)	169.5 (8.0)	168.0 (7.8)	172.3 (12.0)	170.7 (9.2)	158.7 (7.6)	163.8 (8.2)	171.5 (9.0)	175.0 (13.3)	171.3 (14.2)	172.8 (7.6)
Median	168.0	169.0	174.0	170.5	162.0	165.0	173.0	173.0	168.5	170.0
Weight (kg)										
Mean (SD)	65.1 (8.5)	65.0 (9.3)	81.1 (16.9)	75.9 (13.7)	68.8 (7.5)	72.6 (13.9)	73.5 (14.3)	78.8 (18.3)	68.3 (17.1)	81.7 (10.3)
Median	62.4	68.1	76.7	72.9	69.4	74.2	76.0	74.9	65.3	85.4
BMI (kg/m^2)										
Mean (SD)	22.6 (1.3)	23.0 (2.2)	27.3 (4.6)	26.0 (3.3)	27.3 (1.0)	26.9 (3.0)	24.9 (3.6)	25.5 (3.3)	23.0 (2.0)	27.5 (4.5)
Median	22.9	23.0	28.1	25.1	27.1	27.3	25.8	25.2	23.0	27.6

BMI, body mass index; MAD, multiple ascending dose; PBO, placebo.

after multiple doses are reported in **Figure S2** (high-dose) and **Figure S3** (low-dose). The plasma PK parameters for single-dose (day 1) and 14 days of q.d. dosing with ASP3662 are summarized in **Table 4** (high-dose) and **Table 5** (low-dose). Overall, the PKs of ASP3662 and AS2570469 were similar among young Japanese, young non-Japanese, and elderly non-Japanese, although the study was not powered to detect a difference between the populations. Although the single-dose PKs for ASP3662 were nonlinear, steady-state PKs were essentially dose proportional, even for the lower dose levels. However, time to reach steady state and accumulation ratio increased with decreasing dose. At the lowest doses, 0.2 and 0.4 mg ASP3662, steady state was not fully reached after 14 days of q.d. dosing, despite the use of a 3-mg loading dose in the 0.2-mg dose group. Overall, there was no clear dose dependency for CL/F, and the variability (percentage of coefficient of variation) following multiple doses was much lower than that observed for a single dose.

Urine PKs of ASP3662 and AS2570469 were determined only for the 10-mg, 20-mg, and 50-mg cohorts. Small amounts of ASP3662 were recovered from urine (< 0.3% of the administered dose), whereas larger amounts (59.84%) of the metabolite AS2570469 were present, indicating that metabolism of ASP3662 followed by subsequent urinary excretion is an important elimination route.

Exploratory PD results

The renal activity of 11β-HSD2 was determined as the ratio of urinary cortisol/cortisone.[14] The hepatic activity of 11β-HSD1, the most direct molecular target of ASP3662, was obtained by measuring the ratio of 5α + 5β-tetrahydrocortisol/5β-tetrahydrocortisone in urine.[14,15]

Inhibition of 11β-HSD1 by ASP3662 was observed at all dose levels, including the lower doses (0.2–2 mg), following single and multiple dosing (**Figure 1**). There was a high correlation between the 11β-HSD1 ratio results obtained with spot urine samples and the results obtained from 24-hour urine sample collections (data not shown). Inhibition of 11β-HSD1 activity was also observed after single and multiple doses in the high-dose (10-mg, 20-mg, and 50-mg) cohorts (**Figure S5**). Maximal inhibition of 11β-HSD1 (~ 0.1 ratio) approached a nadir at doses of 2 mg ASP3662 and above, suggesting complete 11β-HSD1 inhibition. Interestingly, although significant 11β-HSD1 inhibition was observed for a single 1-mg ASP3662 dose, circulating plasma levels were generally below the lower limit of quantification and, therefore, below the K_i for 11β-HSD1. Inhibition of 11β-HSD1 was long lasting following multiple doses of ASP3662, and the return to baseline 16 days after discontinuation was incomplete even for the lowest dose (0.2 mg). The PDs of ASP3662 were much longer than would be anticipated by its half-life. Despite full and long-lasting 11β-HSD1 inhibition, there were no significant effects on

Table 3 Plasma PK parameters for single-dose ASP3662

Parameter	ASP3662 1 mg (*n* = 6)	ASP3662 3 mg (*n* = 6)	ASP3662 6 mg (*n* = 6)	ASP3662 10 mg (*n* = 6)	ASP3662 30 mg (*n* = 6)	ASP3662 60 mg (*n* = 6)
C_{max} (ng/mL)						
N	6	6	6	6	6	6
Mean (SD)	0.04333 (0.06743)	3.535 (3.885)	27.96 (11.20)	63.96 (15.39)	258.1 (87.14)	594.7 (153.6)
Median	0	1.60	30.49	60.86	239.0	566.3
Min–max	0–0.140	0.380–9.24	10.8–43.7	49.0–93.6	151–386	439–865
T_{max} (hour)						
n	2	6	6	6	6	6
Median	0.75	2.50	1.75	1.75	3.50	3.50
Min–max	0.500–1.00	1.00–4.02	1.00–4.00	1.00–6.00	1.50–4.00	2.00–4.00
CL/F (L/hour)						
n	0	0	6	3	6	6
Mean (SD)	NC	NC	18.38 (9.909)	12.20 (3.403)	10.05 (4.856)	7.933 (2.407)
Median	NC	NC	15.62	10.49	9.012	7.091
Min–max	NC	NC	9.09–35.4	9.99–16.1	4.43–18.4	4.81–11.0
AUC_{inf} (ng·hour/mL)						
n	0	0	6	3	6	6
Mean (SD)	NC	NC	405.1 (187.6)	858.0 (207.2)	3,622 (1,782)	8,186 (2,560)
Median	NC	NC	410.0	953.3	3,372	8,462
Min–max	NC	NC	169–660	620–1,001	1,631–6,766	5,443–12,478
$t_{½}$ (hour)						
n	0	0	6	3	6	6
Mean (SD)	NC	NC	37.74 (7.069)	19.50 (5.101)	17.55 (2.204)	14.81 (1.519)
Median	NC	NC	37.86	21.86	17.38	14.58
Min–max	NC	NC	28.5–46.3	13.7–23.0	14.5–20.2	13.1–17.3

AUC_{inf}, area under the concentration–time curve from predose extrapolated to infinity; CL/F, total oral clearance; C_{max}, maximum concentration; NC, not calculable; PK, pharmacokinetic; $t_{½}$, terminal elimination half-life; T_{max}, time to maximum concentration.

urine cortisol levels (**Figure S4**). However, effects were observed on ACTH, DHEA-s, and 24-hour total urine glucocorticoids (cortisol + cortisone + tetrahydrocortisol (5α + 5β) + tetrahydrocortisone) indicating activation of the HPA axis (**Figure S6**). Although the numbers of subjects are small (*n* = 4), there seemed to be numerically less HPA axis activation at the lowest dose of 0.2 mg ASP3662.

ASP3662 demonstrated specificity for 11β-HSD1 over 11β-HSD2, as no noteworthy changes relative to PBO with regard to the urinary cortisol to cortisone ratio were observed, even at the highest dose of 50 mg ASP3662 following q.d. dosing for 14 days (**Figure S7**).

Safety/tolerability assessments

No deaths, TEAEs leading to discontinuation, serious TEAEs, or drug-related TEAEs occurred in either study. In the SAD study, 18 TEAEs were reported in 14 subjects; all were mild in severity. Medical device site reaction related to the study procedures was the most frequently reported TEAE (**Table S1**).

In the MAD study, 46 TEAEs were reported in 31 subjects (50.0%; **Table 6**); most were mild in severity, except for moderate vasovagal response and benign paroxysmal positional vertigo reported by two young non-Japanese subjects after receiving ASP3662. The most commonly reported TEAE was headache. In the low-dose groups (0.2–2 mg), a single TEAE (headache) was reported in five subjects (ASP3662 0.2 mg, *n* = 2; ASP3662 0.4 mg, *n* = 1; ASP3662 0.7 mg, *n* = 1; and ASP3662 2 mg, *n* = 1).

In both studies, there were no ASP3662-related clinically relevant changes in any clinical laboratory analyses, physical examination, or 12-lead electrocardiogram results, except for clinically significant orthostatic hypotension experienced after a single dose of ASP3662 6 mg. The incidences of potentially clinically significant orthostatic blood pressure measurements in both studies were relatively low and, in general, were not obviously different between the PBO group and the ASP3662 groups, except for in elderly subjects, in which potentially clinically significant orthostatic pulse rate measurements were reported only in subjects who received ASP3662 (44.4%).

There is no clear evidence that ASP3662 has abuse liability or an effect on mood based on the results from the relevant central nervous system scales (Bond-Lader visual analogue scales, Addiction Center Inventory Short Form-49, and Profile of Moods States; data not shown). Slight trends were observed on the subjectively rated scales; however, the variability within treatment groups was relatively large, and overall there was no significant effect of ASP3662 with increasing dose or difference relative to PBO. Additionally, no evidence suggests that ASP3662 has a potential effect on suicidal ideation or behavior.

DISCUSSION

The purpose of this study was to evaluate the safety, tolerability, PKs, and PDs of the novel 11β-HSD1 inhibitor

Table 4 Plasma PK parameters for ASP3662 (PKAS, MAD study part 1 – high-dose cohorts)

Parameter	Young Japanese			Young non-Japanese		Elderly non-Japanese
	10 mg (*n* = 8)	20 mg (*n* = 8)	50 mg (*n* = 8)	20 mg (*n* = 8)	50 mg (*n* = 8)	20 mg (*n* = 9)
Single dose – day 1						
AUC_{inf} (ng·hour/mL)						
n	8	8	8	8	8	9
Mean (SD)	1,278 (529.6)	2,154 (621.3)	7,876 (2,117)	3,014 (1,059)	8,741 (5,009)	3,151 (1,107)
%CV	41.5	28.9	26.9	35.1	57.3	35.1
Median	1,310	2,181	8,014	2,839	7,184	3,045
Min–max	652–1,981	1,332–3,315	5,320–11,616	1,709–4,621	4,954–19,757	1,919–5,260
CL/F (L/hour)						
n	8	8	8	8	8	9
Mean (SD)	9.254 (4.086)	9.993 (2.926)	6.758 (1.787)	7.412 (2.61)	7.005 (2.789)	6.99 (2.152)
%CV	44.2	29.3	26.4	35.2	39.8	30.8
Median	7.651	9.182	6.240	7.279	7.259	6.567
Min–max	5.05–15.3	6.03–15.0	4.30–9.40	4.33–11.7	2.53–10.1	3.8–10.4
C_{max} (ng/mL)						
n	8	8	8	8	8	9
Mean (SD)	91.87 (26.53)	213.0 (47.47)	673.4 (109.3)	232.2 (51.43)	490.9 (94.28)	251.5 (74.74)
%CV	28.9	22.3	16.2	22.1	19.2	29.7
Median	83.42	214.4	680.9	236.2	490.1	233.1
Min–max	62.0–148	138–294	482–852	155–304	341–632	164–406
$t_{½}$ (hour)						
n	8	8	8	8	8	9
Mean (SD)	18.87 (4.402)	18.06 (4.072)	11.33 (2.581)	17.17 (6.014)	13.37 (5.953)	15.92 (2.799)
Median	17.67	18.39	10.07	15.36	11.67	15.55
Min–max	13.2–24.9	12.0–25.5	8.57–15.6	10.5–27.4	8.92–27.6	11.7–21.8
T_{max} (hour)						
n	8	8	8	8	8	9
Median	3.0	1.75	1.25	1.75	3.50	3.0
Min–max	1.5–4.0	1.0–4.0	1.0–8.0	1.0–4.0	2.0–4.0	1.0–4.0
Multiple dose – day 18						
AUC_{tau} (ng·hour/mL)						
n	8	8	8	8	7	9
Mean (SD)	1,954 (878.1)	2,616 (864.7)	7,922 (3,559)	3,488 (1,319)	11,345 (7,221)	3,869 (1,427)
%CV	44.9	33.1	44.9	37.8	63.6	36.9
Median	1,760	2,468	7,615	3,114	8,918	3,525
Min–max	1,014–3,307	1,482–4,478	1,195–13,166	1,951–5,488	5,710–26,917	2,351–7,120
CL/F (L/hour)						
n	8	8	8	8	7	9
Mean (SD)	6.07 (2.591)	8.322 (2.562)	10.46 (12.75)	6.487 (2.372)	5.507 (2.275)	5.675 (1.649)
%CV	42.7	30.8	121.9	36.6	41.3	29.1
Median	5.708	8.117	6.58	6.473	5.607	5.675
Min–max	3.02–9.87	4.47–13.5	3.80–41.8	3.64–10.3	1.86–8.76	2.81–8.51
C_{max} (ng/mL)						
n	8	8	8	8	7	9
Mean (SD)	170.8 (35.92)	293.6 (60.33)	767.1 (331.9)	324.6 (85.45)	834.7 (270.2)	342.1 (84.12)
%CV	21.0	20.5	43.3	26.3	32.4	24.6
Median	172.0	289.6	855.9	313.5	817.3	312.1
Min–max	95.7–211	189–390	90.5–1,106	182–445	588–1,394	244–468
C_{trough} (ng/mL)						
n	8	8	8	8	7	9
Mean (SD)	37.65 (30.42)	34.01 (24.86)	115.3 (59.73)	58.68 (40.91)	261.3 (267.1)	63.58 (49.38)
%CV	80.8	73.1	51.8	69.7	102.2	77.7

(*Continues*)

Table 4 (Continued)

Parameter	Young Japanese			Young non-Japanese		Elderly non-Japanese
	10 mg (*n* = 8)	20 mg (*n* = 8)	50 mg (*n* = 8)	20 mg (*n* = 8)	50 mg (*n* = 8)	20 mg (*n* = 9)
Median	24.76	26.35	103.3	42.71	175.2	52.25
Min–max	13.5–84.0	13.7–92.1	21.0–223	19.9–132	60.4–841	26.1–184
R_{ac} (AUC)						
n	8	8	8	8	7	9
Mean (SD)	2.042 (0.5171)	1.387 (0.1879)	1.181 (0.4289)	1.448 (0.2037)	1.695 (0.6614)	1.498 (0.2775)
%CV	25.3	13.5	36.3	14.1	39.0	18.5
Median	2.039	1.323	1.319	1.42	1.53	1.437
Min–max	1.28–2.72	1.20–1.70	0.165–1.49	1.22–1.82	1.19–3.13	1.17–2.15
$t_{½}$ (hour)						
n	7	7	6	7	7	8
Mean (SD)	24.23 (4.513)	30.02 (9.109)	24.91 (7.405)	22.91 (9.535)	19.87 (6.215)	25.78 (3.437)
Median	23.01	29.79	27.35	21.39	20.88	24.49
Min–max	19.1–32.0	14.5–44.8	12.3–31.7	13.2–39.2	11.4–27.8	21.8–30.9
T_{max} (hour)						
n	8	8	8	8	7	9
Median	2.0	1.5	3.017	1.25	3.0	2.0
Min–max	1.0–4.0	0.5–4.0	1.0–4.0	1.0–3.0	1.0–4.0	1.5–4.0

%CV, percentage of coefficient of variation; AUC_{inf}, area under the concentration–time curve from predose extrapolated to infinity; AUC_{tau}, area under the concentration–time curve for a dosing interval; CL/F, total oral clearance; C_{max}, maximum concentration; C_{trough}, trough concentration; MAD, multiple ascending dose; PK, pharmacokinetic; PKAS, pharmacokinetic analysis set; R_{ac} (AUC), accumulation ratio based on area under the concentration–time curve; $t_{½}$, terminal elimination half-life; T_{max}, time to maximum concentration.

ASP3662. Increased levels of glucocorticoids have been implicated in the development of symptoms of Alzheimer's disease[16–19] and painful diabetic peripheral neuropathy and, as such, 11β-HSD1 is considered an attractive therapeutic target.

The PKs of single-dose ASP3662 were nonlinear, with greater than dose-proportional increase of C_{max} and AUC parameters, an increase of $t_{½}$ with decreasing doses of ASP3662, and a higher variability in PK parameters with lower doses (≤ 6 mg). The fact that the nonlinearity decreased with higher doses suggests that a saturable process is involved. Because this study evaluated ASP3662 administered orally, data on intravenous administration are not available. It is, therefore, uncertain whether a dose-proportional increase in bioavailability contributed to this nonlinear behavior. Interestingly, there was evidence of significant 11β-HSD1 inhibition following a single dose of ASP3662 1 mg even though the plasma levels were below the levels of quantification. There is no evidence to suggest that a transporter is related to ASP3662 bioavailability. ASP3662 may be sequestered in a peripheral tissue, such as the liver or adipose tissue, where 11β-HSD1 is highly expressed, or by nonspecific binding leading to the observed disconnect between the PK and the peripheral PD effects. A similar phenomenon was reported for another 11β-HSD1 inhibitor, ABT-384.[20,21]

Two dose ranges were evaluated in the MAD study. The high-dose range (10–50 mg) was chosen to explore the safety and tolerability of ASP3662 up to the C_{max} and AUC_{24} exposure limits. The low-dose range (0.2–2 mg) was chosen to further characterize the PD and PK of ASP3662. Overall, the PKs of ASP3662 were similar among young Japanese, young non-Japanese, and elderly non-Japanese subjects following single and multiple doses.

Following multiple dosing, the time to ASP3662 steady state was dose dependent, and for doses above 2 mg, steady state was reached between 2 and 11 days of q.d. dosing. For the lowest doses of 0.2 and 0.4 mg, ASP3662 steady state was not fully reached even after 14 days of continuous dosing, despite the 3-mg ASP3662 loading dose for the 0.2-mg ASP3662 treatment group. The accumulation ratio also decreased with increasing dose, and the variability in ASP3662 exposure was much lower with higher doses. Despite the extreme nonlinear single-dose PKs, the steady-state PKs were close to dose proportional. The multiple dose ASP3662 PKs, therefore, also suggested that a saturable process contributes to the nonlinear PKs.

Near complete inhibition of 11β-HSD1, the most direct molecular target of ASP3662, was observed for doses as low as 2 mg and was sustained for much longer than the half-life of ASP3662, which may indicate strong binding to 11β-HSD1. In-house data (not shown) demonstrated that ASP3662 binding was competitive. This long-lasting PD effect is not likely due to the presence of a metabolite, as the principal metabolite (AS2570469) is not active. Inhibition of 11β-HSD1 with ASP3662 resulted in expected activation of the HPA axis due to decreased intracellular conversion of cortisone to cortisol, which apparently involved sites of negative feedback for the release of corticotropin-releasing hormones, such as the hypothalamus and/or the hippocampal formation. There was no obvious impact on circulating cortisol levels, most likely due to a compensatory increased production of cortisol from the adrenals. The observed effect on the HPA axis was dose-related increases in DHEA-s, ACTH, and 24-hour total glucuronides. The modest increases in DHEA-s and ACTH were not considered to be clinically relevant with respect to these relatively short exposures. These results are consistent

with those reported for other 11β-HSD1 inhibitors.[7–10,21–23] However, the implication of chronic administration of a selective 11β-HSD1 inhibitor remains to be assessed as, to date, there have been no clinical trials of treatment with 11β-HSD1 inhibitors longer than 12–24 weeks.[7,8,12,13,24]

Overall, single oral doses up to 60 mg ASP3662 and multiple oral doses up to 50 mg for 14 days seemed to be safe and well tolerated in young Japanese and non-Japanese and elderly non-Japanese subjects. The maximum tolerated dose was not established, and full inhibition of 11β-HSD1

Table 5 Plasma PK parameters for ASP3662 (PKAS, MAD study part 2 – low-dose cohorts)

Parameter	Single dose – day 1		Multiple dose – last day of dosing			
	0.7 mg (*n* = 6)	2 mg (*n* = 6)	0.2 mg (*n* = 4)	0.4 mg (*n* = 4)	0.7 mg (*n* = 6)	2 mg (*n* = 6)
AUC_{tau} (ng·hour/mL)						
n	NC	NC	4	4	6	5
Mean (SD)	NC	NC	16.31 (2.584)	37.07 (2.631)	63.82 (15.89)	215.1 (25.06)
%CV	NC	NC	15.8	7.1	24.9	11.7
Median	NC	NC	16.80	36.93	61.73	218.8
Min–max	NC	NC	13.2–18.5	34.0–40.4	49.5–93.9	175–243
AUC_{inf} (ng·hour/mL)						
n	6[a]	2	NC	NC	NC	NC
Mean (SD)	0.2437 (0.4421)	48.03 (7.87)	NC	NC	NC	NC
%CV	181.5	16.4	NC	NC	NC	NC
Median	0.01242	48.03	NC	NC	NC	NC
Min–max	0–1.11	42.5–53.6	NC	NC	NC	NC
CL/F (L/hour)						
n	NC	2	4	4	6	5
Mean (SD)	NC	42.21 (6.917)	12.51 (2.085)	10.83 (0.7639)	11.44 (2.349)	9.41 (1.208)
%CV	NC	16.4	16.7	7.1	20.5	12.8
Median	NC	42.21	12.01	10.83	11.34	9.139
Min–max	NC	37.3–47.1	10.8–15.2	9.90–11.8	7.45–14.2	8.23–11.4
C_{max} (ng/mL)						
n	6	6	4	4	6	5
Mean (SD)	0.02205 (0.02913)	0.8636 (1.076)	0.9769 (0.2393)	2.956 (0.2460)	6.729 (1.918)	21.17 (5.181)
%CV	132.1	124.6	24.5	8.3	28.5	24.5
Median	0.01261	0.2856	0.9902	2.87	6.938	18.14
Min–max	0–0.0805	0.0779–2.73	0.715–1.21	2.77–3.31	4.32–9.69	17.2–29.3
C_{trough} (ng/mL)						
n	NC	NC	4	4	6	5
Mean (SD)	NC	NC	0.5524 (0.09036)	1.072 (0.1719)	1.389 (0.3190)	3.493 (1.166)
%CV	NC	NC	16.4	16.0	23.0	33.4
Median	NC	NC	0.5573	1.053	1.234	3.437
Min–max	NC	NC	0.443–0.652	0.918–1.26	1.10–1.83	1.80–5.03
T_{max} (hour)						
n	5	6	4	4	6	5
Median	0.5	1.0	3.0	1.25	1.0	1.5
Min–max	0.5–120	1.0–2.0	2.0–12.0	0.5–3.0	1.0–2.0	1.0–4.0
V_zF (L)						
n	NC	2	3	2	1	4
Mean (SD)	NC	5,472 (1,378)	2,888 (2,634)	2,516 (45.89)	3,677 (NC)	1,231 (547.6)
%CV	NC	25.2	91.2	1.8	NC	44.5
Median	NC	5,472	2,005	2,516	3,677	1,165
Min–max	NC	4,498–6,446	809–5,851	2,484–2,549	3,677–3,677	715–1,880
R_{ac} (AUC)						
n	NC	NC	4	2	5	5
Mean (SD)	NC	NC	4.513 (4.477)	6,076 (2,384)	7,264 (5,016)	149.2 (107.1)
%CV	NC	NC	99.2	39.2	69.1	71.8
Median	NC	NC	3.438	6,076	9,238	125.8
Min–max	NC	NC	0.321–10.9	4,391–7,762	1,030–13,388	14.9–311

(*Continues*)

Table 5 (**Continued**)

Parameter	Single dose – day 1		Multiple dose – last day of dosing			
	0.7 mg (*n* = 6)	2 mg (*n* = 6)	0.2 mg (*n* = 4)	0.4 mg (*n* = 4)	0.7 mg (*n* = 6)	2 mg (*n* = 6)
$t_{½}$ (hour)						
n	NC	2	3	2	1	4
Mean (SD)	NC	92.96 (37.86)	181.6 (172.3)	167.9 (14.94)	227.2 (NC)	86.24 (31.35)
Median	NC	92.96	127.8	167.9	227.2	87.56
Min–max	NC	66.2–120	42.6–374	157–178	227–227	55.8–114

%CV, percentage of coefficient of variation; AUC_{inf}, area under the concentration–time curve from predose extrapolated to infinity; AUC_{last}, AUC from predose (time 0) to the time of the last quantifiable concentration; AUC_{tau}, area under the concentration–time curve for a dosing interval; CL/F, total oral clearance; C_{max}, maximum concentration; C_{trough}, trough concentration; MAD, multiple ascending dose; NC, not calculated; PK, pharmacokinetic; PKAS, pharmacokinetic analysis set; R_{ac} (AUC), accumulation ratio based on area under the concentration–time curve; T_{max}, time to maximum concentration; V_ZF, apparent volume of distribution.
[a]AUC_{last} values are presented because AUC_{inf} could not be calculated.

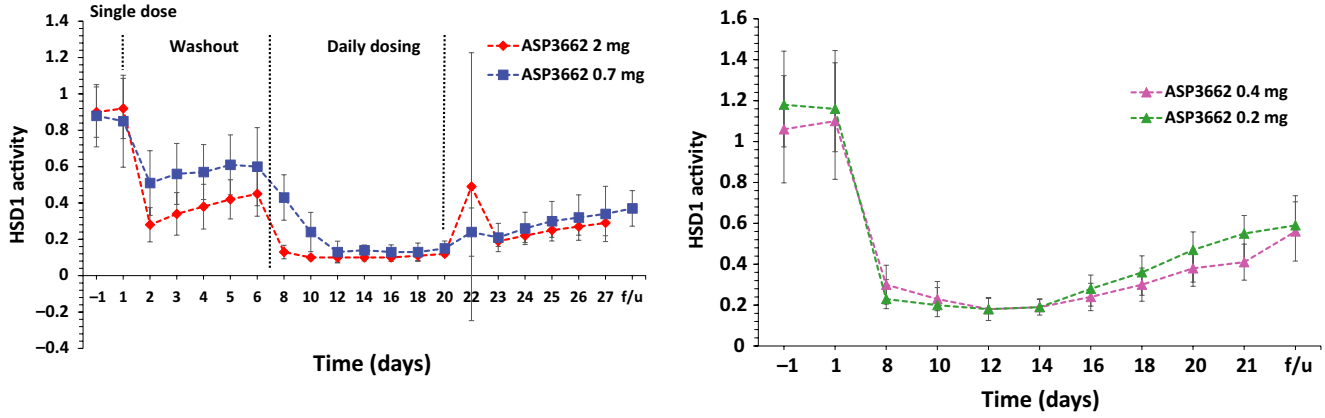

Figure 1 Urine 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) activity from first morning void (part 2 – low-dose). HSD1 activity, ratio of 5α tetrahydrocortisol + 5β tetrahydrocortisol to tetrahydrocortisone. Subjects in the 0.2-mg cohort received a loading dose of 3 mg ASP3662 on day 1 followed by once-daily doses of 0.2 mg from days 2–14.

Table 6 TEAEs occurring in ≥ 5% of subjects (MAD study)

Parameter	PBO (*n* = 13)	ASP3662				Total (*N* = 62)
		10 mg (*n* = 8)	20 mg (*n* = 25)	50 mg (*n* = 16)	Total (*n* = 49)	
Any TEAE, *n* (%)	8 (61.5)	3 (37.5)	14 (56.0)	6 (37.5)	23 (46.9)	31 (50.0)
Number of TEAEs	10	3	21	12	36	46
Drug-related TEAE, *n* (%)	4 (30.8)	2 (25.0)	9 (36.0)	4 (25.0)	15 (30.6)	19 (30.6)
Number of drug-related TEAEs	5	2	12	6	20	25
MedDRA (v 15.1) system organ class preferred term						
Gastrointestinal disorders	2 (15.4)	0	1 (4.0)	2 (12.5)	3 (6.1)	5 (8.1)
Constipation	1 (7.7)	0	1 (4.0)	2 (12.5)	3 (6.1)	4 (6.5)
General disorders and administration site conditions	3 (23.1)	0	3 (12.0)	1 (6.3)	4 (8.2)	7 (11.3)
Medical device site reaction	3 (23.1)	0	2 (8.0)	1 (6.3)	3 (6.1)	6 (9.7)
Nervous system disorders	3 (23.1)	0	9 (36.0)	3 (18.8)	12 (24.5)	15 (24.2)
Headache	1 (7.7)	0	5 (20.0)	3 (18.8)	8 (16.3)	9 (14.5)
Skin and subcutaneous tissue disorders	0	1 (12.5)	0	2 (12.5)	3 (6.1)	3 (4.8)

MAD, multiple ascending dose; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; TEAE, treatment-emergent adverse event.

was achieved with multiple daily doses of 2 mg and above. The safety, tolerability, and PD effects (particularly peripheral 11β-HSD1 inhibition) of ASP3662 are consistent with testing daily maximal doses within a window of 2–10 mg to completely block the target enzyme activity. Therefore, ASP3662 seems to have a large safety margin to study its efficacy in decreasing intracellular cortisol levels. The phase IIa proof-of-concept study testing ASP3662 in patients with painful diabetic peripheral neuropathy (NCT02372578) was terminated early because of futility. There were no safety signals associated with ASP3662 precluding further development.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

Figure S1. Mean plasma concentration curve of ASP3662 in subjects treated with single-dose ASP3662 (PKAS, SAD study).
Figure S2. Mean plasma concentration curves of ASP3662 (**a–c**) and AS2570469 (**d–f**) after multiple high doses (day 18) of ASP3662 in young Japanese (**a,d**), young, non-Japanese (**b,e**), and elderly, non-Japanese (**c,f**) subjects (PKAS, MAD study, Part 1).
Figure S3. Mean plasma concentration curve of ASP3662 on the last day of dosing after multiple low doses of ASP3662 (PKAS, MAD study, Part 2).
Figure S4. Urine cortisol levels from first morning void (Part 2 – low dose).
Figure S5. Peripheral 11β-HSD1 activity based on cumulative amount excreted (A_e) of tetrahydrocortisols (5α + 5β)/5β-tetrahydrocortisone in urine in young Japanese (**a**), young, non-Japanese (**b**), and elderly, non-Japanese (**c**) subjects on days 1 and 18.
Figure S6. Endocrine clinical laboratory assessments of the HPA axis (Plasma, Part 2 – Low Dose).
Figure S7. Peripheral HSD2 activity based on urine cortisol/cortisone ratio in urine in young Japanese (**a**), young, non-Japanese (**b**), and elderly, non-Japanese (**c**) subjects on days 1 and 18.
Table S1. Treatment-emergent adverse events occurring in ≥ 5% of subjects (SAD study).

Acknowledgments. Medical writing support was provided by OPEN Health Medical Communications (Chicago, IL) and was funded by Astellas Pharma Global Development. The authors acknowledge the study principal investigator, David Han, and the staff at PAREXEL International (Glendale, CA).

Funding. This study was funded by Astellas Pharma Global Development.

Conflict of Interest. M.W., W.K., and G. J. M. are employed by Astellas. S.B., N.Y., and T.W. were employed by Astellas at the time this study was conducted.

Author Contributions. S.B., M.W., T.W., W.K., N.Y., and G.J.M. wrote the manuscript. S.B., M.W., and N.Y. designed the research. M.W., T.W., and G.J.M. performed the research. S.B., M.W., T.W., W.K., N.Y., and G.J.M. analyzed the data.

1. Rajan, V., Edwards, C.R. & Seckl, J.R. 11 beta-Hydroxysteroid dehydrogenase in cultured hippocampal cells reactivates inert 11-dehydrocorticosterone, potentiating neurotoxicity. *J. Neurosci.* **16**, 65–70 (1996).
2. Tomlinson, J.W. *et al.* 11beta-hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr. Rev.* **25**, 831–866 (2004).
3. White, P.C., Mune, T. & Agarwal, A.K. 11 beta-Hydroxysteroid dehydrogenase and the syndrome of apparent mineralocorticoid excess. *Endocr. Rev.* **18**, 135–156 (1997).
4. Kiso, T., Sekizawa, T., Uchino, H., Tsukamoto, M. & Kakimoto, S. Analgesic effects of ASP3662, a novel 11beta-hydroxysteroid dehydrogenase 1 inhibitor, in rat models of neuropathic and dysfunctional pain. *Br. J. Pharmacol.* **175**, 3784–3796 (2018).
5. Scott, J.S., Goldberg, F.W. & Turnbull, A.V. Medicinal chemistry of inhibitors of 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1). *J. Med. Chem.* **57**, 4466–4486 (2014).
6. Vitku, J. *et al.* Endocrine disruptors and other inhibitors of 11beta-hydroxysteroid dehydrogenase 1 and 2: tissue-specific consequences of enzyme inhibition. *J. Steroid Biochem. Mol. Biol.* **155**, 207–216 (2016).
7. Feig, P.U. *et al.* Effects of an 11beta-hydroxysteroid dehydrogenase type 1 inhibitor, MK-0916, in patients with type 2 diabetes mellitus and metabolic syndrome. *Diabetes Obes. Metab.* **13**, 498–504 (2011).
8. Rosenstock, J. *et al.* The 11-beta-hydroxysteroid dehydrogenase type 1 inhibitor INCB13739 improves hyperglycemia in patients with type 2 diabetes inadequately controlled by metformin monotherapy. *Diabetes Care* **33**, 1516–1522 (2010).
9. Heise, T. *et al.* Safety, efficacy and weight effect of two 11beta-HSD1 inhibitors in metformin-treated patients with type 2 diabetes. *Diabetes Obes. Metab.* **16**, 1070–1077 (2014).
10. Stefan, N. *et al.* Inhibition of 11beta-HSD1 with RO5093151 for non-alcoholic fatty liver disease: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol.* **2**, 406–416 (2014).
11. Gibbs, J.P. *et al.* Population pharmacokinetic/pharmacodynamic model of subcutaneous adipose 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) activity after oral administration of AMG 221, a selective 11beta-HSD1 inhibitor. *J. Clin. Pharmacol.* **51**, 830–841 (2011).
12. Shah, S. *et al.* Efficacy and safety of the selective 11beta-HSD-1 inhibitors MK-0736 and MK-0916 in overweight and obese patients with hypertension. *J. Am. Soc. Hypertens.* **5**, 166–176 (2011).
13. Marek, G.J. *et al.* Efficacy and safety evaluation of HSD-1 inhibitor ABT-384 in Alzheimer's disease. *Alzheimers Dement.* **10**, S364–S373 (2014).
14. Rasmuson, S. *et al.* Increased glucocorticoid production and altered cortisol metabolism in women with mild to moderate Alzheimer's disease. *Biol. Psychiatry* **49**, 547–552 (2001).
15. Courtney, R. *et al.* Modulation of 11beta-hydroxysteroid dehydrogenase (11betaHSD) activity biomarkers and pharmacokinetics of PF-00915275, a selective 11betaHSD1 inhibitor. *J. Clin. Endocrinol. Metab.* **93**, 550–556 (2008).
16. Csernansky, J.G. *et al.* Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. *Am. J. Psychiatry* **163**, 2164–2169 (2006).
17. Green, K.N., Billings, L.M., Roozendaal, B., McGaugh, J.L. & LaFerla, F.M. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. *J. Neurosci.* **26**, 9047–9056 (2006).
18. Popp, J. *et al.* Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. *Neurobiol. Aging* **36**, 601–607 (2015).
19. Young, A.H., Sahakian, B.J., Robbins, T.W. & Cowen, P.J. The effects of chronic administration of hydrocortisone on cognitive function in normal male volunteers. *Psychopharmacology* **145**, 260–266 (1999).
20. An, G. *et al.* Population pharmacokinetics of the 11beta-hydroxysteroid dehydrogenase type 1 inhibitor ABT-384 in healthy volunteers following single and multiple dose regimens. *Biopharm. Drug Dispos.* **35**, 417–429 (2014).
21. Liu, W. *et al.* Clinical safety, pharmacokinetics, and pharmacodynamics of the 11beta-hydroxysteroid dehydrogenase type 1 inhibitor ABT-384 in healthy volunteers and elderly adults. *Clin. Pharmacol. Drug Dev.* **2**, 133–151 (2013).
22. Sandeep, T.C. *et al.* 11Beta-hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc. Natl. Acad. Sci. USA* **101**, 6734–6739 (2004).
23. Tomlinson, J.W. *et al.* Inhibition of 11beta-hydroxysteroid dehydrogenase type 1 activity in vivo limits glucocorticoid exposure to human adipose tissue and decreases lipolysis. *J. Clin. Endocrinol. Metab.* **92**, 857–864 (2007).
24. Chiodini, I. *et al.* Cortisol secretion in patients with type 2 diabetes: relationship with chronic complications. *Diabetes Care* **30**, 83–88 (2007).