

# Clinical Bioavailability of the Novel BACE1 Inhibitor Lanabecestat (AZD3293): Assessment of Tablet Formulations Versus an Oral Solution and the Impact of Gastric pH on Pharmacokinetics

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## Abstract

The relative bioavailability of lanabecestat administered as 2 tablet formulations versus an oral solution was investigated. This phase I single-center, open-label, randomized, 3-period crossover study involved healthy male and nonfertile female subjects aged 18–55 years (NCT02039180). Subjects received a single 50-mg lanabecestat dose as solution, tablet A, or tablet B on day 1 of each crossover period; 14 of 16 subjects completed the study. Relative bioavailability based on plasma lanabecestat  $AUC_{0-\infty}$  (area under the plasma drug concentration–time curve from zero to infinity) geometric mean ratio versus oral solution (primary variable) was: tablet A, 1.052 (90% confidence interval [CI], 1.001–1.106); tablet B, 1.040 (0.989–1.093). These 90% CIs for geometric mean ratios are within accepted standard bioequivalence boundaries for all other pharmacokinetic (PK) parameters for both lanabecestat and metabolite (AZI3569724). All 3 formulations had similar plasma lanabecestat concentration–time profiles. Six adverse events were reported by 6 subjects (37.5%, all mild). GastroPlus modeling predicted a negligible impact of gastric pH changes on systemic PK (up to pH 7.4). Both tablet formulations fall within standard accepted bioequivalence criteria versus the oral solution. A single 50-mg lanabecestat dose was well tolerated as a solution or tablet formulation in this population.

## Keywords

Alzheimer's, AZD3293, BACE1, bioavailability, pharmacokinetics

Alzheimer's disease (AD) is a devastating progressive degenerative disease resulting from pathological changes in the brain because of loss of neurons.<sup>1</sup> AD manifests as progressive memory impairment accompanied by gradual decline in other cognitive abilities, culminating in complete functional dependence.<sup>1,2</sup> AD and other dementias are a global health challenge,<sup>3</sup> recently estimated to affect more than 46.8 million people and their families worldwide.<sup>4</sup> With 9.9 million new cases diagnosed each year and an aging global population, it is predicted that AD and other dementias will affect 131.5 million people by 2050.<sup>4</sup> There is currently a paucity of effective pharmacotherapy for patients with AD, as approved drugs have only limited efficacy in improving symptomatology, and they do not treat the underlying cause of the disease.<sup>5,6</sup> This has led to a global research effort to identify new treatments that act on the

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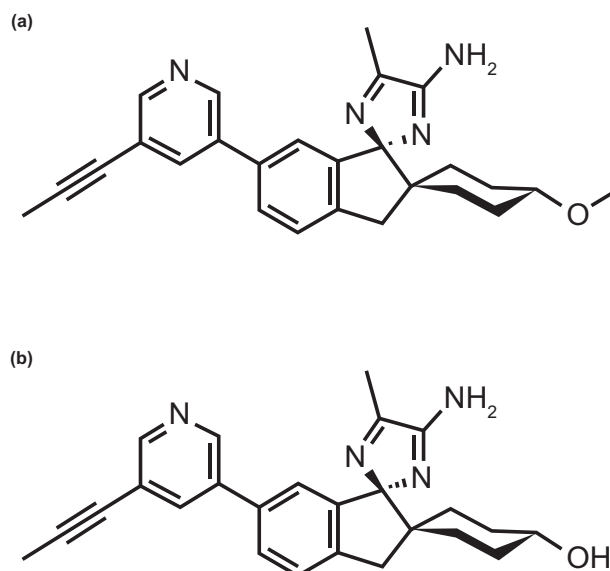
No authors are fellows of the American College of Clinical Pharmacology (FCP).

underlying pathophysiology of AD and have the potential to modulate disease progression.

Alzheimer's disease is characterized by the existence of 2 pathological features, namely, amyloid plaques and neurofibrillary tangles,<sup>1,7</sup> which form as a result of the aggregation of amyloid- $\beta$  ( $A\beta$ ) in the brain as postulated by the amyloid cascade hypothesis.<sup>8</sup> Amyloid accumulation results because of changes in the production, processing, and/or clearance of brain  $A\beta$  peptides.<sup>1</sup>  $A\beta$  is produced by the sequential cleavage of amyloid precursor protein (APP) to  $A\beta$  peptides via beta-secretase 1 (BACE1), which releases the soluble N-terminal fragment of APP (sAPP $\beta$ ).<sup>1</sup>  $\gamma$ -Secretase then cuts the C-terminal fragment C99 to release  $A\beta$ , which is secreted from the cell.<sup>1</sup> Cleavage by BACE1 is the rate-limiting step for the production of  $A\beta$ ,<sup>9</sup> making it a key target for therapeutic intervention to inhibit  $A\beta$  production and theoretically slow disease progression.<sup>10,11</sup> Further support for the pivotal role of BACE1 in the pathophysiology of AD originates from genetic evidence, with more than 200 autosomal-dominant missense mutations identified in the genes for APP and presenilin (the  $\gamma$ -secretase catalytic subunit) that are associated with familial AD.<sup>12</sup> Notably, both causative and protective mutations in APP expression around the BACE1 cleavage site have been described.<sup>7,10,11</sup> In transgenic mouse models, the Swedish mutation K670N/M671L increases APP susceptibility to BACE cleavage and confers early-onset AD,<sup>13</sup> whereas the A673T APP variant reduces APP susceptibility to BACE cleavage and is associated with a reduced risk for AD in elderly individuals.<sup>14</sup>

Recent research efforts in AD have focused on the development of small nonpeptidic BACE1 inhibitors, which, compared with older agents, have improved molecular weight, favorable pharmacokinetic (PK) parameters, and sufficient lipophilicity to cross the blood-brain barrier (BBB).<sup>12,15</sup> Most recently, orally bioavailable BACE1 inhibitors have been developed that can cross the BBB and have demonstrated robust cerebral  $A\beta$  reduction in preclinical animal models.<sup>12</sup> Several of these compounds have been investigated in clinical trials.<sup>12,16,17</sup>

Lanabecestat (AZD3293; LY3314814; [1*r*,1'*R*,4*R*]-4-methoxy-5''-methyl-6'-[5-(prop-1-yn-1-yl)pyridin-3-yl]-3'*H*-dispiro[cyclohexane-1,2'-indene-1',2''-imidazol]-4''-amine) is a potent, brain-permeable selective human BACE1 inhibitor that is in development for the treatment of early AD.<sup>18</sup> AZ13569724 is the major circulating lanabecestat metabolite.<sup>18,19</sup> The chemical structures are shown in Figure 1. Following a single oral dose of [<sup>14</sup>C]-lanabecestat, 74% of the radioactive dose was recovered in feces and 25% in urine.<sup>18,19</sup> Lanabecestat is an orally active compound with a slow off-rate from its target enzyme BACE1, which



**Figure 1.** Chemical structure of (a) lanabecestat (1*r*,1'*R*,4*R*)-4-methoxy-5''-methyl-6'-[5-(prop-1-yn-1-yl)pyridin-3-yl]-3'*H*-dispiro[cyclohexane-1,2'-indene-1',2''-imidazol]-4''-amine) and (b) AZ13569724, the major circulating metabolite.

robustly reduced plasma, cerebrospinal fluid (CSF), and brain  $A\beta$ 1–40,  $A\beta$ 1–42, and sAPP $\beta$  concentrations in vitro and in vivo in mouse, guinea pig, and dog models.<sup>18</sup> The lanabecestat in vitro 50% inhibitory concentration (IC<sub>50</sub>) for BACE1 is 0.6 nM, and the mean Caco-2 apical-to-basolateral Papp permeability is  $34.8 \times 10^{-6}$  cm/s.<sup>18</sup> Previous studies have shown that in vivo potency correlates well with in vitro potency, as determined in primary neurons.<sup>20</sup> The BACE1 potency of metabolite AZ13569724 is approximately one-tenth that of lanabecestat, and circulating concentrations at steady state are approximately one-third those of the parent. Collectively, these data suggest that the metabolite AZ13569724 has minimal contribution to in vivo  $A\beta$  reduction following lanabecestat administration.

The results of 2 randomized, double-blind, placebo-controlled single- and multiple-ascending-dose (SAD/MAD) studies, which evaluated a range of lanabecestat doses using an oral solution, have recently been reported.<sup>21</sup> The studies in elderly healthy subjects and patients with mild to moderate AD showed no safety or tolerability concerns up to the highest lanabecestat dose evaluated (750 mg single dose or 150 mg multiple dose). The plasma lanabecestat half-life was 11–24 hours in the SAD study, suggesting that lanabecestat is suitable for once-daily dosing. PK results were similar in young and elderly healthy subjects.<sup>21</sup> In the MAD study, similar PK findings were also observed in healthy elderly subjects and patients with AD, with a  $t_{\max}$  of 1.1 to 2.5 hours and a mean  $t_{1/2}$  of 16 to 21 hours across the 15- to 150-mg dose

range in patients with AD.<sup>21</sup> Furthermore, lanabecestat produced prolonged suppression of plasma and CSF A $\beta$  peptides in these populations by using a once-weekly (70-mg) dosing schedule.<sup>21</sup> Based on these findings, lanabecestat was progressed to later-stage clinical development as a potential disease-modifying treatment for AD, and recruitment of patients with AD into 2 global phase 3 studies is now ongoing (NCT02245737; AMARANTH and NCT02783573; DAYBREAK-ALZ).

In preparation for phase 3 evaluation of lanabecestat, solid (tablet) formulations were developed that differ slightly in their components and percentages of individual excipients. An oral tablet, especially one administered once daily that has reasonable bioavailability is of value from a compliance and ease-of-administration perspective in a chronic disease, compared with intramuscularly delivered<sup>22</sup> or multiple-daily-dose drugs.<sup>23,24</sup> Of 2 lanabecestat doses selected for later-stage development (20 and 50 mg once daily), the 50-mg dose was used in the present study because it was the highest dose proposed for use in the phase 3 studies. Exposure following a 50-mg dose was expected to be well within the range of exposures shown to be generally well tolerated in young and elderly healthy subjects in the SAD and MAD studies.<sup>21</sup>

The primary objectives of this study were to investigate the relative bioavailability of lanabecestat following administration of 2 tablet formulations versus the oral solution and to evaluate basic PK parameters for lanabecestat and its major metabolite (AZ13569724). A PK modeling approach was also used to predict changes in bioavailability with differing gastric pH levels.

## Methods

### Study Population

Healthy male and nonfertile female subjects aged 18 to 55 years with a body mass index of  $\geq 19$  to  $\leq 30$  kg/m<sup>2</sup> and who provided informed consent were eligible to participate in the study dependent on the results of physical examination, clinical laboratory evaluation, and medical history. Subjects were excluded if they had a history of any clinically significant disease or disorder, including the presence of gastrointestinal, hepatic, or renal disease or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs; a history of previous or ongoing psychiatric or neurological disease/condition; known or suspected drug or alcohol abuse/dependence; frequent use of tobacco or nicotine-containing products; excessive consumption of caffeine; any clinically significant abnormalities in clinical chemistry (including the liver enzymes alanine aminotransferase, aspartate amino-

transferase, and alkaline phosphatase), hematology or urinalysis; taken any prescribed or nonprescribed drugs or herbal medicines within 2 weeks of administration of lanabecestat; or a history of hypersensitivity/severe allergy to drugs. In addition, subjects could not use any of the following drugs within 3 weeks prior to the first administration of lanabecestat: any drug with enzyme-inducing properties or known to be a strong inhibitor or inducer of cytochrome P450 3A4 and any drug known to be a strong inhibitor of P-glycoprotein. Subjects were also excluded if they had any intake of grapefruit- or Seville orange-containing foods or products within 7 days of the first administration of the study drug.

The study was conducted in a clinical pharmacology unit at WCCT Global Phase I unit in Cypress, California, in accordance with the Declaration of Helsinki,<sup>25</sup> International Conference on Harmonisation/Good Clinical Practice,<sup>26</sup> applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples. The study was approved and overseen by Alpha Institutional Review Board, San Clemente, California.

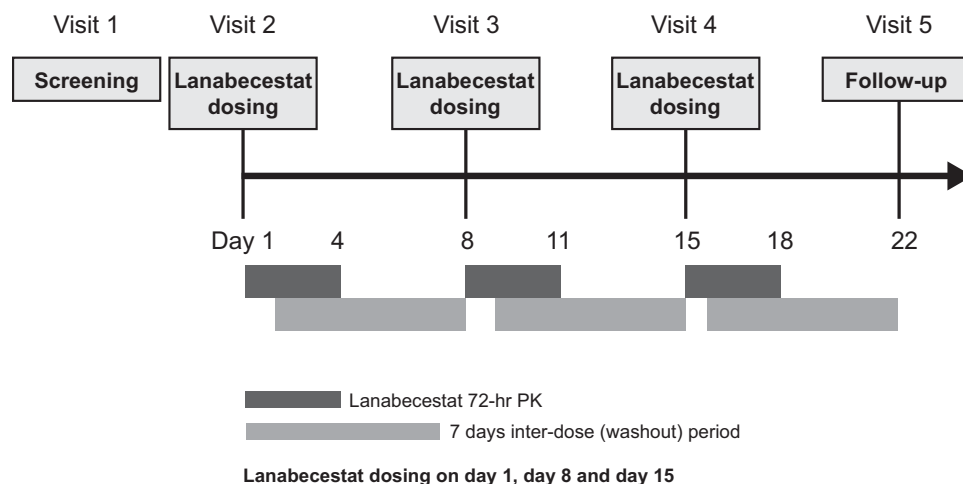
### Study Objectives

The primary objective of the study was to estimate the relative bioavailability of lanabecestat after administration via 2 tablet formulations (tablet A and tablet B), compared with an oral solution (based on plasma lanabecestat concentration, as measured by the area under the plasma drug concentration–time curve from zero to infinity [AUC<sub>0–∞</sub>]). Basic PK parameters of the tablet formulations, compared with the oral solution of lanabecestat, were also evaluated. Secondary objectives included the evaluation of the safety and tolerability of lanabecestat in healthy subjects. In addition, the observed PK parameters were also used to conduct modeling of the effects of varying gastric pH levels on drug absorption (up to pH 7.4).

### Study Design

This was a phase 1 single-center, open-label, randomized, 3-period crossover study in healthy male and nonfertile female subjects (NCT02039180; Figure 2). Screening evaluations occurred during the 3-week period prior to study drug administration. Three single doses of lanabecestat (2 different tablet formulations [50 mg formulation A; 50 mg formulation B] and a 10-mL oral solution [5 mg/mL]) were administered as a single dose on days 1, 8, and 15, with a washout period of at least 1 week (7–10 days) between the doses. Randomization determined the order of treatments. Total study time was a maximum of 48 days for all subjects who completed all 3 treatments of the crossover.

All treatments were administered after an overnight fast of  $\geq 10$  hours with dosage forms taken with



Random assignment of three formulations across the three lanabecestat doses

**Figure 2.** Study design.

240 mL (230 mL water plus 10 mL of the oral solution dosage form for a total water intake of 240 mL) of noncarbonated, room-temperature water at approximately the same time on each treatment day. With the exception of its use for drug administration, water was restricted from 1 hour before to 1 hour after drug administration. For those subjects randomized to the oral solution, water was used to rinse the container holding the oral solution, and those rinses along with the remainder of the 230 mL of water were consumed. Subjects were fasted until 4 hours postdose.

Stable concomitant medication was permitted provided such therapy was not expected to change during the study, was agreed to be acceptable, and was judged to not interfere with study objectives or safety. Paracetamol for occasional pain relief ( $\leq 3$  g/day), nonprescription adrenergic nasal sprays for relief of nasal congestion, and hormone replacement therapy were permitted. All other concomitant medication or therapy was not permitted.

Serial venous blood samples (3 mL) for the measurement of plasma lanabecestat and AZ13569724 (major lanabecestat metabolite) concentrations were collected predose (15 or 30 minutes) and at regular intervals up to 72 hours postdose starting on days 1, 8, and 15. Sensitive liquid chromatography–tandem mass spectrometry assays using a Shimadzu LC-20AD coupled with an API 5000 triple quadrupole mass spectrometer were developed and validated in human plasma, plasma ultrafiltrate, CSF, and urine for lanabecestat and AZ13569724. Stable-isotope-labeled lanabecestat and AZ13569724 were used as internal standards. Plasma samples were extracted by protein precipitation. Plasma ultrafiltrate was prepared using a Centrifree® centrifugal ultrafiltration device with

a 30-kDa molecular-weight cutoff. CHAPS (0.2 M, 5  $\mu$ L) was added to 250  $\mu$ L plasma in each vial prior to transferring samples to the ultrafiltration device.

Calibration curves were validated for lanabecestat and AZ13569724 in human biological matrices (ie, plasma, urine, plasma ultrafiltrate, and CSF).<sup>27</sup> The dilution range was evaluated up to 10-fold in urine and up to 100-fold in plasma. The accuracy and precision of the methods were assessed in multiple analytical batches using multiple replicates of quality controls, and the overall performance met preset criteria. The methods demonstrated acceptable selectivity from matrices for the quantitation of lanabecestat and the metabolite AZ13569724 in human plasma and plasma ultrafiltrate, and minimal matrix effects were observed with high recovery of both analytes and internal standards. Furthermore, the presence of hemolyzed red blood cells or elevated lipid (fat) levels in human plasma did not affect the quantitation of lanabecestat and AZ13569724 in the plasma method. The stability of lanabecestat and the metabolite AZ13569724 was investigated in a variety of matrices and under a variety of conditions. Both analytes demonstrated acceptable stability under controlled conditions. Full details of the analytical method have been previously published.<sup>27</sup>

PK parameters were derived using noncompartmental methods with Phoenix WinNonlin 6.2 or later (Certara L.P. [Pharsight], St Louis, Missouri). PK variables calculated for lanabecestat and AZ13569724 were: maximum observed plasma drug concentration ( $C_{max}$ ), time to maximum plasma drug concentration ( $t_{max}$ ), area under plasma drug concentration–time curve from zero to time  $t$ , the last quantifiable concentration ( $AUC_{0-t}$ ),  $AUC_{0-\infty}$ , half-life associated with the terminal elimination rate constant ( $t_{1/2\lambda_z}$ ), and oral



clearance (CL/F). The lower limit of quantification (LLOQ) for lanabecestat was 0.5 ng/mL. For plasma drug concentrations and all PK parameters (except  $t_{\max}$ ), arithmetic and geometric means were reported. In addition, the relative bioavailability for tablets versus the oral solution (based on AUC) was calculated.

Safety monitoring was conducted throughout the study, including adverse events (AEs), clinical laboratory evaluation, vital signs, electrocardiogram (ECG), physical (including neurological) examination, and Columbia Suicide Severity Rating Scale (C-SSRS) assessment.

### *PK Modeling to Assess Changes in Bioavailability With Differing Gastric pH Levels*

To evaluate the potential impact of elevated gastric pH on clinical PK, an absorption model was constructed using the physiochemical properties of lanabecestat with observed clinical PK results. GastroPlus (Simulations Plus, Inc., Lancaster, California) is a mechanistically based simulation software package that simulates absorption and pharmacokinetics in humans and animals and has been used to model the absorption behavior of drugs.<sup>28–30</sup> A preliminary absorption model was constructed using a combination of *in silico* and *in vitro* physiochemical properties. Properties included solubility in a range of media (aqueous buffer solution, pH 7.4 [37°C]: 0.05 mg/mL; 0.1 M HCl [25°C]: >10 mg/mL; aqueous oral solution, pH 2.5, used in phase 1 clinical studies [25°C]: >10 mg/mL), dissociation constant (pKa [base] 6.4 and 3.8), distribution coefficient (log D pH 7.4: 2.0 [octanol/water]), and permeability (Caco-2 Papp >10 × 10<sup>-6</sup> cm/s; predicted human permeability [hPeff] 3.0 × 10<sup>-4</sup> cm/s). A solution dosage form was used in the initial clinical evaluation of lanabecestat. For simulations of the tablet formulations used in subsequent studies, the *in vitro* dissolution profile of the tablet was inputted. Plasma lanabecestat concentration–time profiles were simulated by linking this absorption model to a 2-compartmental drug disposition model that had been fitted to the observed clinical data. The simulated profile following administration with an elevated gastric pH (ie, pH 7.4) was compared with the observed exposure in the fasted state.

### *Statistical Analysis*

A sample size of 12 healthy subjects was expected to be sufficient to detect a 20% difference in bioavailability for the primary variable, the AUC<sub>0–∞</sub> on the natural log scale. Calculation of sample size was based on data from a previous study conducted to assess the safety, effects on the body, and blood/plasma and urine drug concentrations of a single 50-mg dose of lanabecestat (NCT01739647). The estimate was based on

a bioequivalence pair-wise comparison of each tablet formulation with the oral solution formulation using  $\alpha = 0.05$  and 90% power within the framework of a 3-period crossover study. No correction was made for 2 tablet formulations being compared with the oral solution. To help ensure that 12 subjects would complete all 3 crossover periods, 16 subjects were enrolled and randomized. The PK analysis set included all subjects who received lanabecestat and who had evaluable PK data. Subjects who completed 2 crossover visits were evaluable for the bioavailability comparison. All subjects who received ≥1 dose of lanabecestat and had postdose data available were included in the safety population.

All PK data were graphically illustrated and presented by descriptive statistics. Relative bioavailability of lanabecestat for the tablet formulations was computed by the geometric mean ratio of dose-corrected tablet versus oral solution AUC<sub>0–∞</sub>, including 90% confidence interval (CI). Natural-log-transformed AUC<sub>0–∞</sub> was analyzed using a mixed-effects model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. This analysis was performed using PROC MIXED from the SAS Institute. Estimates of the adjusted mean differences and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (tablets A and B/oral solution) and 90% CIs for the ratios.

## **Results**

### *Study Population Characteristics*

Fifty-four healthy subjects were screened (February 4–17, 2014). In total, 16 healthy subjects, 13 men and 3 women, with a mean ± standard deviation (SD) age of 39.3 ± 9.89 years (Table 1), were enrolled in the study, with 14 subjects completing all 3 periods of the study. Two subjects chose to discontinue the study, one prior to receiving tablet A, and the other prior to receiving tablet B; neither subject received the oral solution. During the study, 1 subject was noted as taking paracetamol during treatment with tablet A.

### *PK Results*

In total, 14 subjects completed all 3 treatment periods, with 15 subjects evaluable for PK in the groups that received either lanabecestat tablet A or tablet B formulation and 14 subjects evaluable for PK who received the lanabecestat oral solution.

Relative bioavailability based on lanabecestat AUC<sub>0–∞</sub> geometric mean ratio versus oral solution (primary end point) was: tablet A, 1.052 (90%CI, 1.001–1.106); tablet B, 1.040 (90%CI, 0.989–1.093).

**Table 1.** Study Population Demographics and Baseline Characteristics

Characteristic	All Subjects (n = 16)
Age (years)	
Mean (SD)	39.3 (9.89)
Range	24, 54
Sex, n (%)	
Male	13 (81.3)
Female	3 (18.8)
Race, n (%)	
American Indian/Alaska native	1 (6.3)
Asian	1 (6.3)
Black or African American	7 (43.8)
White	6 (37.5)
Other	1 (6.3)
Ethnicity, n (%)	
Hispanic or Latino	2 (12.5)
Not Hispanic or Latino	14 (87.5)

SD, standard deviation.

The 90% CIs for geometric mean ratios of tablet A or tablet B versus oral solution were completely contained within the standard accepted bioequivalence boundaries for all other PK parameters for both lanabecestat and AZ13569724 (Table 2, Figures 3 and 4).

Plasma lanabecestat concentration–time profiles (72 hours postdose) for all 3 formulations were very similar and visually indistinguishable (Figure 5A). Plasma lanabecestat concentrations were above the LLOQ (0.5 ng/mL) by 0.5 hours postdose (day 1) in all subjects and remained above the LLOQ for up to 72 hours postdose (day 4). A semilogarithmic plot of the mean plasma lanabecestat concentrations (ng/mL) from baseline through 72 hours postdose for all 3 formulations demonstrated that the elimination was of first order, as the profiles were linear through the observed terminal phase (Figure 5B).

#### Assessment of Potential Impact of Elevated Gastric pH on Clinical PK

Varying gastric pH (up to 7.4) was predicted to have had a negligible impact on clinical PK and was thought to be driven by the low dose (50 mg) as well as the high intestinal permeability (Figure 6).

#### Safety and Tolerability

All 16 subjects were included in the safety analysis set (Table 3). A total of 6 AEs were reported by 6 treated subjects (37.5%) in the study. AEs were reported by 3 subjects (18.8%) receiving tablet A, 1 subject (6.3%) receiving tablet B, and 2 subjects (12.5%) receiving the oral solution. All AEs were assessed as mild. There were no deaths or serious AEs in the study, and no subjects discontinued as a result of AEs.

Treatment-emergent AEs (TEAEs) in subjects receiving tablet A included dry skin, headache, and upper respiratory tract infection (URTI), 1 subject each (6.3%), of which the URTI was considered possibly related to the study drug. Headache was reported by 1 subject (6.3%) receiving tablet B and was considered possibly related to the study drug. Dizziness and dry skin were reported by subjects receiving the oral solution (1 subject each [6.3%]).

There were no significant changes in clinical laboratory evaluation, including hematology, clinical chemistry (including liver enzymes), or urinalysis during the study. Changes in vital signs as well as ECGs, physical examination, neurological examination, and C-SSRS findings were all unremarkable, and no significant trends were noted. Potentially clinically significant vital sign measurements were observed in 5 subjects at various points over the study, but these were not associated with symptoms, and none were considered clinically significant by the study investigator.

## Discussion

This study was designed to evaluate the relative bioavailability of the 2 tablet formulations compared with the oral solution. It demonstrated that the tablet A and tablet B formulations met standard accepted bioequivalence criteria of a 90% CI range from 0.8 to 1.25,<sup>31,32</sup> relative to the oral solution evaluated. The 90% CIs for the AUC<sub>0–∞</sub> geometric mean ratios and all other PK parameters of tablet A or tablet B versus the oral solution were completely contained within those bioequivalence boundaries for lanabecestat. These data suggest that patients who receive lanabecestat will have the same exposure when the drug is administered as one of these tablets or the oral solution.

Plasma lanabecestat concentration–time profiles were similar for all 3 formulations. The plasma lanabecestat half-life was comparable in the 2 tablets and oral solution formulation studied at approximately 16 hours for each. In the MAD study, similar PK findings were also observed in healthy elderly subjects and patients with AD, with a mean half-life of 16 to 21 hours across the 15- to 150-mg dose range assessed in patients with AD.<sup>21</sup> The plasma lanabecestat half-life was 11 to 24 hours in the SAD study, and PK results were similar in young (18–55 years) and elderly (55–80 years) healthy subjects.<sup>21</sup> A very slow off-rate of lanabecestat from BACE1 (half-life of approximately 9 hours) was observed in *in vitro* studies, which could result in a prolonged reduction of Aβ peptide concentrations, driven more by the turnover rate of the BACE1 enzyme than the recovery rates of Aβ1-40, Aβ1-42, and sAPPβ.<sup>18</sup> Indeed, the SAD study demonstrated prolonged suppression, up to 3 weeks,

**Table 2.** PK Parameters for Each Treatment Group

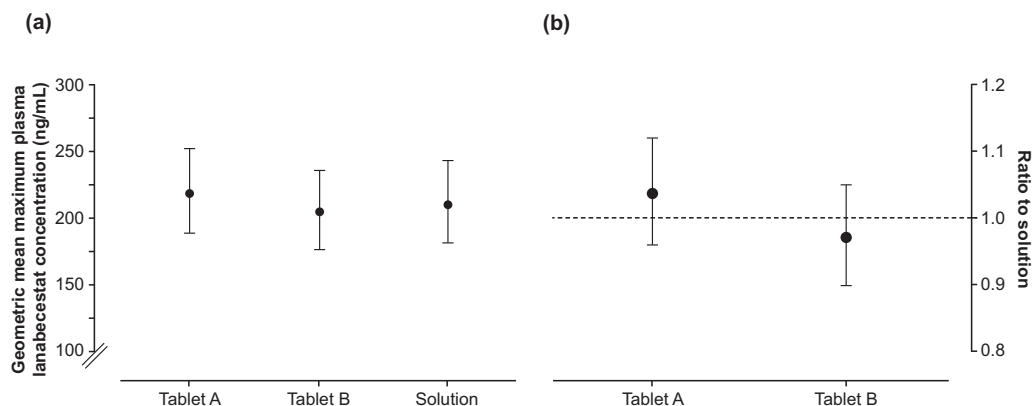
Parameter	Lanabecestat 50 mg (n = 14)			Ratio of Tablet A to Oral Solution	Ratio of Tablet B to Oral Solution
	Tablet A	Tablet B	Oral Solution		
<b>Lanabecestat AUC<sub>0-∞</sub> (ng·h/mL)</b>					
Geometric mean	2949.1	2915.1	2803.9	1.052	1.040
90%CI	(2670.788– 3256.427)	(2641.079– 3217.636)	(2537.247– 3098.620)	(1.001–1.106)	(0.089–1.093)
Arithmetic mean (SD)	3066.0 (563.988)	2963.3 (659.5)	2901.0 (653.1)		
<b>Lanabecestat AUC<sub>0-t</sub> (ng·h/mL)</b>					
Geometric mean	2836.5	2809.9	2696.4	1.052	1.042
90%CI	(2566.809– 3134.529)	(2543.753– 3103.910)	(2438.103– 2982.158)	(1.001–1.106)	(0.991–1.096)
Arithmetic mean (SD)	2945.9 (551.6)	2857.3 (646.0)	2788.5 (635.9)		
<b>AZ13569724 AUC<sub>0-t</sub> (ng·h/mL)</b>					
Geometric mean	667.6	668.4	673.6	0.991	0.992
90%CI	(586.814– 759.428)	(587.729– 760.060)	(591.647– 766.818)	(0.939–1.046)	(0.940–1.048)
Arithmetic mean (SD)	736.1 (200.5)	711.2 (229.4)	749.1 (216.1)		
<b>Lanabecestat C<sub>max</sub> (ng/mL)</b>					
Geometric mean	218.6	204.7	211.0	1.036	0.970
90%CI	(188.729– 253.192)	(176.847– 236.948)	(181.909– 244.676)	(0.959–1.119)	(0.898–1.049)
Arithmetic mean (SD)	235.7 (74.5)	215.7 (81.8)	227.7 (75.0)		
<b>AZ13569724 C<sub>max</sub> (ng/mL)</b>					
Geometric mean	43.3	42.3	47.2	0.916	0.896
90%CI	(37.309–50.202)	(36.539–49.065)	(40.631–54.901)	(0.829–1.012)	(0.811–0.991)
Arithmetic mean (SD)	47.5 (14.2)	44.2 (13.0)	52.0 (15.0)		
<b>Lanabecestat t<sub>1/2λz</sub> (h)</b>					
Geometric mean	15.9	15.9	16.4	0.970	0.969
90%CI	(15.059–16.755)	(15.054–16.734)	(15.506–17.285)	(0.932–1.010)	(0.931–1.010)
Arithmetic mean (SD)	16.2 (2.7)	16.0 (2.3)	16.54 (2.6)		
<b>Lanabecestat CL/F (L/h)</b>					
Geometric mean	17.0	17.2	17.8	0.951	0.962
90%CI	(15.354–18.721)	(15.539–18.932)	(16.136–19.706)	(0.904–0.999)	(0.915–1.011)
Arithmetic mean (SD)	16.9 (3.2)	17.7 (4.0)	18.0 (3.6)		

AUC<sub>0-∞</sub>, area under the plasma drug concentration–time curve from zero to infinity; AUC<sub>0-t</sub>, area under plasma drug concentration–time curve from zero to time t, the last quantifiable concentration; CI, confidence interval; CL/F, oral clearance; C<sub>max</sub>, maximum observed plasma drug concentration; SD, standard deviation; t<sub>1/2λz</sub>, half-life associated with the terminal elimination rate constant.

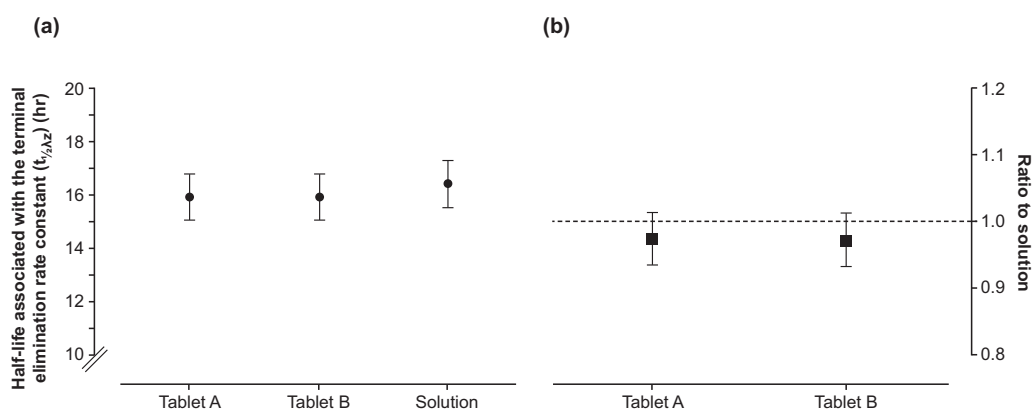
of plasma Aβ peptides by lanabecestat following a single dose at the highest dose studied, and the MAD study demonstrated prolonged suppression of plasma Aβ with a once-weekly (70 mg) dosing schedule.<sup>21</sup> Collectively, these data suggest that lanabecestat would be amenable to once-daily dosing.

A study into the effect of food consumption on the PK of lanabecestat concluded that the drug could

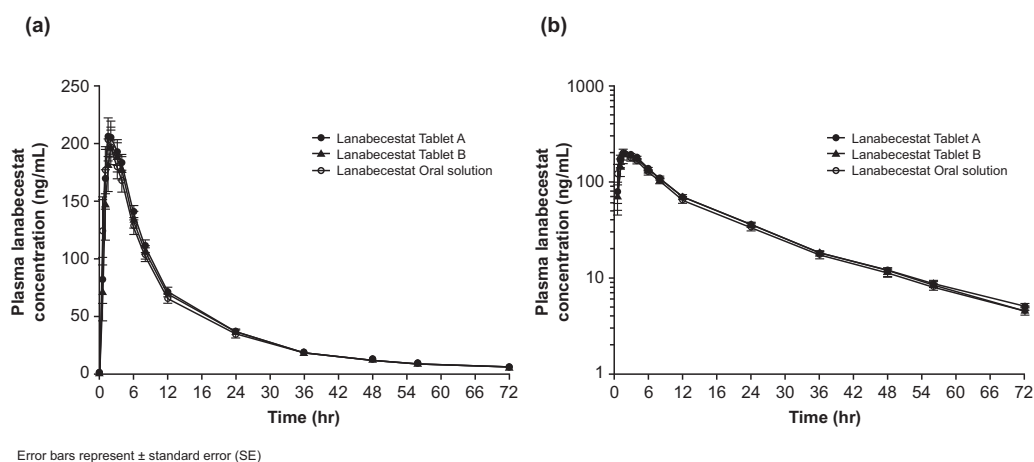
be taken with or without food.<sup>21</sup> Food intake led to a later t<sub>max</sub> (~2 hours) and modest reduction in C<sub>max</sub> (701 and 499 ng/mL under fasted and fed conditions, respectively, after a single 150-mg dose), but a minimal effect on AUC. These observations are consistent with physiological changes such as gastric-emptying time that occur between the fasted and fed states. PK/pharmacodynamic modeling of the phase 1 data



**Figure 3.** (a) Geometric mean maximum plasma lanabecestat concentration ( $C_{max}$ , ng/mL)  $\pm$  90%CI; (b) ratios of tablet formulations to oral solution geometric mean plasma lanabecestat  $C_{max}$  (ng/mL)  $\pm$  90%CI.



**Figure 4.** (a) Geometric mean half-life associated with plasma lanabecestat terminal elimination rate constant ( $t_{1/2\lambda_z}$ ) values (hours)  $\pm$  90%CI; (b) ratios of tablet formulations to oral solution  $t_{1/2\lambda_z}$  values (hours)  $\pm$  90%CI.



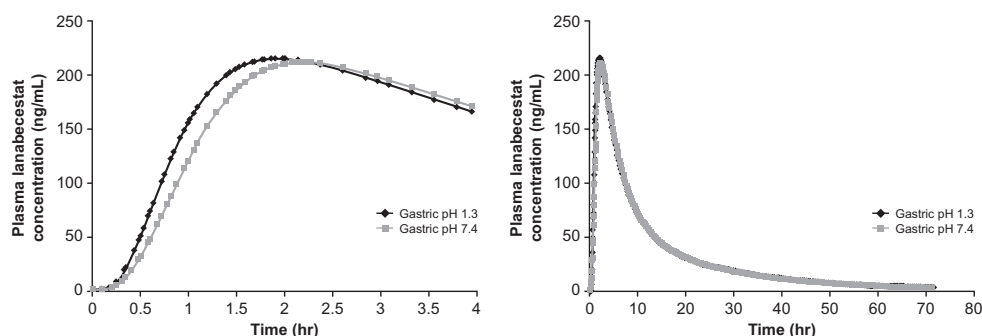
**Figure 5.** (a) Arithmetic mean plasma lanabecestat concentration–time profiles  $\pm$  SEs for the 3 formulations; (b) profiles with semilogarithmic concentration scale  $\pm$  SEs.

suggests that any effects of food on plasma lanabecestat exposure would not impact safety or CSF  $A\beta$  reductions.<sup>21</sup>

Lanabecestat has high permeability and pH-dependent solubility and could tentatively be consid-

ered as a Biopharmaceutical Classification System II drug. Absorption modeling using GastroPlus predicted that changes in gastric pH (up to pH 7.4) would be expected to have a negligible effect on clinical PK. This is likely driven by the relatively low dose (50 mg) and





**Figure 6.** Plasma lanabecestat concentration–time profile simulations following oral dosing with a 50-mg tablet of lanabecestat at varying gastric pHs.

**Table 3.** TEAEs for Each Treatment Group

TEAE, n (%)	Lanabecestat Tablet A (n = 16)	Lanabecestat Tablet B (n = 16)	Lanabecestat Oral Solution (n = 16)	Lanabecestat All Subjects (n = 16)
Number of subjects with ≥ 1 TEAE	3 (18.8)	1 (6.3)	2 (12.5)	6 (37.5)
URTI	1 (6.3)	0	0	1 (6.3)
Dizziness	0	0	1 (6.3)	1 (6.3)
Headache	1 (6.3)	1 (6.3)	0	2 (12.5)
Dry skin	1 (6.3)	0	1 (6.3)	2 (12.5)

TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

the compound's high passive intestinal permeability, which creates sink conditions in vivo. These data are expected to have clinical significance given that gastric acid secretion diminishes with aging.<sup>33</sup> Because of the low dose and its physiochemical properties, the absorption of lanabecestat is not expected to show sensitivity to the types of physiological changes that may be present in the target patient population.

Overall, lanabecestat was well tolerated in this population of healthy subjects. This finding concurs with the results of other recent studies in healthy young and elderly subjects and patients with mild to moderate AD, in whom no safety or tolerability concerns were identified up to the highest doses given (a single dose of up to 750 mg or multiple daily doses of up to 150 mg for 2 weeks).<sup>21</sup> Importantly, the present study also demonstrated no significant changes in liver-related clinical chemistry parameters with lanabecestat treatment. Clinical development of another BACE1 inhibitor, LY2886721, was terminated during phase 2 as a result of elevations in circulating liver-enzyme activity in a small number of subjects through a mechanism that appeared to be unrelated to BACE1 inhibition.<sup>12</sup>

This study was designed to allow evaluation of tablet versus oral solution of lanabecestat in healthy subjects aged 18 to 55 years to facilitate the advancement of clinical development. Although both tablet formulations met the standard accepted criteria for bioequivalence to the oral solution, the tablet B

formulation was selected for use in the phase 3 AMARANTH trial (NCT02245737), primarily for manufacturability reasons. The AMARANTH trial is a multicenter randomized, double-blind, placebo-controlled study to evaluate the disease-modifying potential of lanabecestat at daily doses of 20 or 50 mg over 2 years. The study is being conducted in ~2200 patients with mild cognitive impairment because of AD or mild AD.

## Conclusions

This study shows that both tablet formulations of lanabecestat evaluated met the standard accepted criteria for bioequivalence compared with the oral solution. Plasma lanabecestat concentrations and its major metabolite, AZ13569724, were similar for all 3 formulations across all times, suggesting that they do not differ in a clinically meaningful manner. PK modeling of the effects of gastric pH on drug PK demonstrated that changes in gastric pH are predicted to have a minimal effect on clinical exposure. A 50-mg lanabecestat dose was generally well tolerated when administered as an oral solution or as either tablet formulation in this population. Based on the results of the present study and the SAD and MAD studies,<sup>21</sup> lanabecestat is being evaluated in 2 phase 3 trials in patients with early AD (NCT02245737 AMARANTH; NCT02783573 DAYBREAK-ALZ). These studies

will assess the disease-modifying potential of this promising new treatment.

### Declaration of Conflicting Interests

N. Ye, P. Daga, L.B. Rosen, J. Mullen, M.C. Minkwitz, and A.R. Kugler were employees of AstraZeneca when this research was conducted. In addition, A.R. Kugler and J. Mullen report ownership of shares in AstraZeneca. S.A.M. and D.M.B. are employees of and report ownership of shares in Eli Lilly and Company.

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