2. SYNOPSIS

NAME OF SPONSOR/COMPANY Achillion Pharmaceuticals, Inc. **NAME OF FINISHED PRODUCT** ACH-0144471 **NAME OF ACTIVE INGREDIENT** ACH-0144471	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**

Title of Study:	A Three-Part Phase 1 Study to Evaluate the Potential Drug Interaction between ACH-0144471 and Warfarin, Bupropion, and Ethinyl Estradiol and Norethindrone (Oral Contraceptive) in Healthy Adult Subjects
Investigator:	PPD
Study Center:	PPD PPD USA
Publication (Reference):	Not applicable.

Studied Period: **PHASE OF DEVELOPMENT**: 1

(date of first enrollment)
First subject screened – 10 July 2019
(date of last completed)
Actual last subject last visit – 06 November 2019

Objectives:

Primary Objectives

Part 1 (Drug Interaction between ACH-0144471 and Warfarin)
To determine the effect of multiple doses of ACH-0144471 on the single-dose PK of R- and S-warfarin.

Part 2 (Drug Interaction between ACH-0144471 and Bupropion)
To determine the effect of multiple doses of ACH-0144471 on the single-dose PK of bupropion and hydroxybupropion.

Part 3 (Drug Interaction between ACH-0144471 and Ethyl Estradiol (EE)/Norethindrone (NET) [Oral Contraceptive (OC)])
To determine the effect of multiple doses of ACH-0144471 on the single-dose PK of EE/NET (OC).

Secondary Objectives

Part 1 (Drug Interaction between ACH-0144471 and Warfarin)
To determine the effect of multiple dose ACH-0144471 on the single-dose pharmacodynamics (PD) of warfarin as assessed by INR.

To assess the safety and tolerability of multiple doses of ACH-0144471 when coadministered with a single dose of warfarin.

Part 2 (Drug Interaction between ACH-0144471 and Bupropion)
To assess the safety and tolerability of multiple doses of ACH-0144471 when coadministered with a single dose of bupropion.

Part 3 (Drug Interaction between ACH-0144471 and EE/NET [OC])
To assess the safety and tolerability of multiple doses of ACH-0144471 when coadministered with a single dose of EE/NET (OC).

Exploratory Objectives

Part 1 (Drug Interaction between ACH-0144471 and Warfarin)
To determine the effect of a single dose of warfarin on the multiple-dose PK of ACH-0144471.

Part 2 (Drug Interaction between ACH-0144471 and Bupropion)
To determine the effect of a single dose of bupropion on the multiple-dose PK of ACH-0144471.

Part 3 (Drug Interaction between ACH-0144471 and EE/NET [OC])
To determine the effect of a single dose of EE/NET (OC) on the multiple-dose PK of ACH-0144471.

Endpoints
PK parameters were determined for drug substrates and metabolites (warfarin [Part 1], bupropion and hydroxybupropion [Part 2], and EE and NET [Part 3]) as applicable, i.e., plasma Cmax, Tmax, AUC0-t, AUC0-inf, CL/F (parent only), Kel, and t½.

INR PD parameters were determined in Part 1 only: INR AUC0-168 and INRmax.

PK parameters were determined for plasma ACH-0144471 including AUC0-8, Cmax, Tmax, and plasma trough concentration (Ctrough).

The safety endpoints included the following safety assessments: adverse events (AEs), clinical laboratory evaluations, vital sign measurements, and 12-lead electrocardiograms (ECGs).

Methodology:
This was a 3-part study with each part being an open-label, fixed sequence, 2-period study in healthy adult subjects. Part 1, Part 2, and Part 3 of the study overlapped but subjects were enrolled separately for each part of the study and the order of the parts was determined according to the needs of the ACH-0144471 development program.

Part 1
In each period, subjects were confined to the clinic from Day -1, at the time indicated by the clinical research unit (CRU), and until after the 72-hour PK and PD sample collections and study procedures following dosing on Day 1 of Period 1 and after study procedures on Day 12 of Period 2. Subjects returned for study procedures as indicated in the Schedule of Assessments (SoA).

On Day 1 of Period 1, subjects received a single dose of warfarin, followed by PK blood sampling for R- and S-warfarin and PD blood sampling for PT/INR over 168 hours postdose, as specified in the SoA. In Period 2, subjects received ACH-0144471 every 8 hours (TID) on Days 1 through 11. On the morning of Day 5, ACH-0144471 was coadministered with a single dose of warfarin. PK blood samples were collected for ACH-0144471 predose on Days 1, 3, 4, and 5, and over 8 hours following the morning doses on Days 4 and 5. PK blood samples were collected for R- and S-warfarin and PD blood samples for PT/INR levels over 168 hours postdose on Day 5. See PK and PD blood sampling as specified in the SoA. There was a washout period of at least 14 days between the dose of warfarin in Period 1 and the first dose of ACH-0144471 in Period 2.

Part 2
In each period, subjects were confined to the clinic from Day -1, at the time indicated by the CRU, and until after the 24-hour PK sample collection and study procedures following dosing on Day 1 of Period 1 and after study procedures on Day 9 of Period 2. Subjects returned for study procedures as indicated in the SoA.

On Day 1 of Period 1, subjects received a single dose of bupropion, followed by PK blood sampling for bupropion and hydroxybupropion over 96 hours postdose as specified in the SoA. In Period 2, subjects received ACH-0144471 TID on Days 1 through 8. On the morning of Day 5, ACH-0144471 was coadministered with a single dose of bupropion. PK blood samples were collected for ACH-0144471 predose on Days 1, 3, 4, and 5, and over 8 hours following the morning doses on Days 4 and 5. PK blood samples were collected for bupropion and hydroxybupropion over 96 hours postdose on Day 5. See PK blood sampling as specified in the SoA. There was a washout period of at least 7 days between the dose of bupropion in Period 1 and the first dose of ACH-0144471 in Period 2.

Part 3
In each period, subjects were confined to the clinic from Day -1, at the time indicated by the CRU, and until after the 24-hour PK sample collection and study procedures following dosing on Day 1 of Period 1 and after study procedures on Day 9 of Period 2. Subjects returned for study procedures as indicated in the SoA.

On Day 1 of Period 1, subjects received a single dose of EE/NET (OC), followed by PK blood sampling for EE/NET over 96 hours postdose as specified in in the SoA. In Period 2, subjects received ACH-0144471 TID on Days 1 through 8. On the morning of Day 5, ACH-0144471 was coadministered with a single dose of EE/NET (OC). PK blood samples were collected for ACH-0144471 predose on Days 1, 3, 4, and 5, and over 8 hours following the morning doses on Days 4 and 5. PK blood samples were collected for EE/NET over 96 hours postdose on Day 5. See PK blood sampling as specified in the SoA. There was a washout period of at least 7 days between the dose of EE/NET (OC) in Period 1 and the first dose of ACH-0144471 in Period 2.

Number of Subjects (Planned and Analyzed):
A total of 52 subjects were enrolled in the study, and 50 subjects completed the study.
In Part 1: 12 subjects who were enrolled and completed the study were included in the PK and PD analyses. In Part 2: 16 subjects who were enrolled and completed the study were included in the PK analysis. In Part 3: 24 subjects were enrolled. Data from 24 subjects who completed Period 1 (Treatment E) and 22 subjects who completed Period 2 (Treatment F) of the study were included in the PK analysis. Two (2) subjects were discontinued prior to dosing in Period 2 and thus were not included in Period 2 PK analysis. All subjects were included in the safety analysis.

Diagnosis and Main Criteria for Inclusion:
All subjects enrolled in this study were judged by the Principal Investigator (PI) to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Test Product, Dose, Duration, Mode of Administration, and Batch Number:
In each study part, treatments for Period 1 and Period 2 were administered in a fixed sequence as described below. All study drugs were administered orally with approximately 240 mL of room temperature water under fed conditions.

Part 1
In Period 1, subjects received Treatment A: 25 mg COUMADIN® (Warfarin Sodium Tablets, USP) (2 x 10 mg tablets (Lot No.: AAW6887A1) + 1 x 5 mg tablet (Lot No.: AAY7337A1)). In Period 2, subjects received Treatment B: 200 mg ACH-0144471 (2 x 100 mg tablets (Lot No.: L0607636)) TID on Days 1 - 11, with a single dose of 25 mg COUMADIN® (Warfarin Sodium Tablets, USP) (2 x 10 mg tablets (Lot No.: AAW6887A1) + 1 x 5 mg tablet (Lot No.: AAY7337A1)) coadministered on the morning of Day 5.

Part 2
In Period 1, subjects received Treatment C: 100 mg bupropion hydrochloride (1 x 100 mg tablet (Lot No.: 3089951)) at Hour 0 on Day 1. In Period 2, subjects received Treatment D: 200 mg ACH-0144471 (2 x 100 mg tablets (Lot No.: L0607636)) administered TID on Days 1 - 8, with a single dose of bupropion hydrochloride (1 x 100 mg tablet (Lot No.: 3089951) coadministered on the morning of Day 5.

Part 3
In Period 1, subjects received Treatment E: ALYACEN 1/35 (Norethindrone and Ethinyl Estradiol Tablets USP) (1 x 1 mg/0.035 mg fixed-dose combination tablet (Lot No.: 20190137)) at Hour 0 on Day 1. In Period 2, subjects received Treatment F: 200 mg ACH-0144471 (2 x 100 mg tablets (Lot No.: L0607636)) administered TID on Days 1 - 8, with a single dose of ALYACEN 1/35 (Norethindrone and Ethinyl Estradiol Tablets USP) (1 x 1 mg/0.035 mg fixed-dose combination tablet (Lot No.: 20190137)) on the morning of Day 5.

All parts:
TID ACH-0144471 doses were administered approximately at Hour 0, Hour 9, and Hour 15 with doses taken within 30 minutes of the beginning of respective meals/snacks. Hour 0 in each day was within ±1 hour relative to Hour 0 on Day 1.

Duration of Treatment:

Part 1

The total planned duration of participation for each subject was approximately 67 days including a screening period of approximately 28 days. Subjects were confined to the clinical site for 4 days, from check-in (Day -1) to Day 4 in Period 1 and from check-in (Day -1) to Day 12 in Period 2. There was a washout period of at least 14 days between dosing of warfarin in Period 1 and first dose of ACH-0144471 in Period 2.

Part 2

The total planned duration of participation for each subject was approximately 57 days including a screening period of approximately 28 days. Subjects were confined to the clinical site for 2 days, from check-in (Day -1) to Day 2 in Period 1 and from check-in (Day -1) to Day 9 in Period 2. There was a washout period of at least 7 days between dosing of bupropion in Period 1 and first dose of ACH-0144471 in Period 2.

Part 3

The total planned duration of participation for each subject was approximately 57 days including a screening period of approximately 28 days. Subjects were confined to the clinical site for 2 days, from check-in (Day -1) to Day 2 in Period 1 and check-in (Day -1) to Day 9 in Period 2. There was a washout period of at least 7 days between dosing of EE/NET in Period 1 and first dose of ACH-0144471 in Period 2.

All Parts

All subjects who received at least one dose of study drug (including subjects who terminated the study early) returned to the CRU 14 (± 2) days after the last study drug administration for follow-up procedures, and to determine if any AE had occurred since the last study visit.

Criteria for Evaluation:

Pharmacokinetics:

All Parts

Serial blood samples for assay of plasma concentrations of ACH-0144471 were collected from subjects at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours post first daily ACH-0144471 dose on Days 4 and 5 and prior to first daily dose on Days 1 and 3 (Parts 1, 2, and 3).

Part 1

Serial blood samples for assay of plasma concentrations of R- and S-warfarin were collected from subjects at predose and 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post warfarin dose on Day 1 (Period 1) and Day 5 (Period 2).

Part 2

Serial blood samples for assay of plasma concentrations of bupropion and hydroxybupropion were collected from subjects at predose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, and 96 hours post bupropion dose on Day 1 (Period 1) and Day 5 (Period 2).

Part 3

Serial blood samples for assay of plasma concentrations of EE and NET were collected from subjects at predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours post EE/NET dose on Day 1 (Period 1) and Day 5 (Period 2).

PK Parameters:

Plasma ACH-01444 (Parts 1, 2, and 3): The following PK parameters were determined from 0 - 8 hours data plasma ACH-0144471 concentration data on Days 4 and 5: AUC0-8, Cmax, Tmax, and Ctrough.

The following PK parameters were determined for plasma R- and S-warfarin (Part 1), plasma bupropion and hydroxybupropion (Part 2), and plasma EE and NET (Part 3): AUC0-t, AUC0-inf, Cmax, Tmax, CL/F (except hydroxybupropion), Kel, t½, and MR AUC0-inf (hydroxybupropion only).

Pharmacodynamics:

Part 1
Serial blood samples for assay of blood concentrations of INR were collected from subjects at predose and 0.5, 2, 4, 12, 24, 48, 72, 120, 168 hours (Treatment A only), and 171 hours (Treatment B only) post warfarin dose on Day 1 (Period 1) and Day 5 (Period 2).

The following PD parameters were determined for blood INR: INR AUC0-168 and INRmax.

Safety:
Safety was evaluated by clinical laboratory tests, vital signs, 12-lead ECGs, and AEs.

Statistical Methods:

Pharmacokinetics:

For plasma concentrations and PK parameters, the following summary statistics were calculated: sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum were calculated for all nominal concentration time points and all PK parameters. In addition, geometric mean [Geom Mean] and geometric CV% [Geom CV%] were calculated for PK and PD parameters only.

Analysis of Variance: The drug-drug interaction (DDI), i.e., effect of ACH-0144471 on R- and S-warfarin (Part 1), on bupropion (Part 2), and on EE/NET (Part 3) were investigated in this study. The DDI was assessed using an analysis of variance (ANOVA) approach on the natural-log (ln)-transformed Cmax, AUC0-t, and AUC0-inf of R- and S-warfarin (Part 1), bupropion and hydroxybupropion (Part 2), EE and NET (Part 3), and Cmax and AUC0-8 of ACH-0144471 (all parts). The ANOVA model included treatment as a fixed effect and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference.

Effect of ACH-0144471 on R- and S-warfarin (Part 1), Bupropion (Part 2), and EE/NET (Part 3):
Ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed R-warfarin, S-warfarin, bupropion, hydroxybupropion, EE, and NET Cmax, AUC0-t, and AUC0-inf when coadministered with multiple doses of ACH-0144471 versus when administered alone. The 90% confidence intervals (CIs) for the ratios were derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the analyses on the ln-transformed R-warfarin, S-warfarin,

bupropion, hydroxybupropion, EE, and NET Cmax, AUC0-t, and AUC0-inf when coadministered with multiple doses of ACH-0144471 versus when administered alone. The comparisons of interest were as follows:

- **Part 1:**
  Comparison 1a (R-warfarin): Treatment B2 (ACH-0144471 + warfarin) / Treatment A (warfarin alone)
  Comparison 1b (S-warfarin): Treatment B2 (ACH-0144471 + warfarin) / Treatment A (warfarin alone);
- **Part 2:**
  Comparison 2a (bupropion): Treatment D2 (ACH-0144471 + bupropion) / Treatment C (bupropion alone)
  Comparison 2b (hydroxybupropion): Treatment D2 (ACH-0144471 + bupropion) / Treatment C (bupropion alone);

- **Part 3:**
  Comparison 3a (EE): Treatment F2 (ACH-0144471 + EE/NET) / Treatment E (EE/NET alone)
  Comparison 3b (NET): Treatment F2 (ACH-0144471 + EE/NET) / Treatment E (EE/NET alone).

Effect of R-warfarin and S-warfarin (Part 1), Bupropion and Hydroxybupropion (Part 2), EE and NET (Part 3) on ACH-0144471:

Ratios of LSM and corresponding 90% CIs were also similarly calculated for ACH-0144471 Cmax and AUC0-8 when coadministered with warfarin, bupropion, and EE/NET versus when administered alone. The comparisons of interest were as follows:

- **Part 1**
  Comparison 4 (ACH-0144471): Treatment B2 (ACH-0144471 + warfarin) / Treatment B1 (ACH-0144471 alone)
- **Part 2**
  Comparison 5 (ACH-0144471): Treatment D2 (ACH-0144471 + bupropion) / Treatment D1 (ACH-0144471 alone);
- **Part 3**
  Comparison 6 (ACH-0144471): Treatment F2 (ACH-0144471 + EE/NET)/ Treatment F1 (ACH-0144471 alone);

The ANOVA analysis for Comparisons 1 through 6 were performed immediately after sub-setting the data according to study part.

The inferential results (LSMs, difference between LSMs, and 90% CIs of the difference) were exponentiated to the original scale. Geometric LSMs, geometric mean ratios (GMR), and 90% CIs were presented.

Comparisons of Tmax Between Treatments

The median differences in Tmax were calculated. The comparisons of interest for the median difference in R- and S-warfarin (Part 1), bupropion and hydroxybupropion (Part 2), EE and NET (Part 3) Tmax were as follows:

Effect of ACH-0144471 on R- and S-warfarin (Part 1), Bupropion (Part 2), EE/NET (Part 3):

The comparisons of interest for the median difference in R- and S-warfarin, bupropion, and EE/NET Tmax were as follows:

- **Part 1:**
  Comparison 7a (R-warfarin Tmax): Treatment B2 (ACH-0144471 + warfarin) / Treatment A (warfarin alone)
  Comparison 7b (S-warfarin Tmax): Treatment B2 (ACH-0144471 + warfarin) / Treatment A (warfarin alone);
- **Part 2:**
  Comparison 8a (bupropion Tmax): Treatment D2 (ACH-0144471 + bupropion) / Treatment C (bupropion alone)
  Comparison 8b (hydroxybupropion Tmax): Treatment D2 (ACH-0144471 + bupropion) / Treatment C (bupropion alone);
- **Part 3:**
  Comparison 9a (EE Tmax): Treatment F2 (ACH-0144471 + EE/NET) / Treatment E (EE/NET alone)
  Comparison 9b (NET Tmax): Treatment F2 (ACH-0144471 + EE/NET) / Treatment E (EE/NET alone).

Effect of R-warfarin and S-warfarin (Part 1), Bupropion and Hydroxybupropion (Part 2), EE and NET (Part 3) on ACH-0144471:

The comparisons of interest for the median difference in ACH-0144471 Tmax were as follows:

- **Part 1**
  Comparison 10 (ACH-0144471 Tmax): Treatment B2 (ACH-0144471 + warfarin) / Treatment B1 (ACH-0144471 alone)
- **Part 2**
  Comparison 11 (ACH-0144471 Tmax): Treatment D2 (ACH-0144471 + bupropion) / Treatment D1 (ACH-0144471 alone);
- **Part 3**
  Comparison 12 (ACH-0144471 Tmax): Treatment F2 (ACH-0144471 + EE/NET)/ Treatment F1 (ACH-0144471 alone);

The non-parametric Wilcoxon Signed Rank tests were used and 90% CI and the p-value were presented. The 90% CIs were constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Rank test statistic.

Pharmacodynamics:

Summary statistics for blood INR measurements and PD parameters were calculated and presented as described for plasma concentrations and PK parameters.

A similar mixed-model ANOVA that is described in above for Part 1 PK (Comparison 1) was used to evaluate the effect of ACH-0144471 on INR AUC0-168 and INRmax. Summary ratios of LSM and 90% CIs for the ratios of INR AUC0-168 and INRmax (warfarin with ACH-0144471 versus warfarin alone) were estimated.

Safety:
No inferential statistics were performed.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Part 1 (Plasma R-Warfarin):
The statistical comparisons of plasma R-warfarin PK parameters AUC0-t, AUC0-inf, and Cmax and the non-parametric comparisons of R-warfarin Tmax are summarized in the following tables.

Statistical Comparisons of Plasma R-Warfarin Pharmacokinetic Parameters Following ACH-0144471 TID + Warfarin Versus Warfarin Alone (Part 1) (Pharmacokinetic Population)

	ACH-0144471 TID + Warfarin (Test)		Warfarin Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	78090	12	74930	12	104.22	101.49 - 107.02	3.62
AUC0-inf (ng*hr/mL)	85800	12	83360	12	102.93	99.68 - 106.28	4.38
Cmax (ng/mL)	1327	12	1252	12	106.03	101.96 - 110.27	5.35

ACH-0144471 TID + Warfarin: 200 mg ACH-0144471 administered orally TID on Days 1-11 with 25 mg warfarin coadministered on Day 5 (test)
Warfarin Alone: 25 mg warfarin administered orally on Day 1 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
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Based on GMR values, peak and extent of exposure to R-warfarin were similar (differences of approximately 3% to 6%) following the coadministration of warfarin with ACH-0144471 compared to administration of warfarin alone. The 90% CIs of GMR for AUC0-t, AUC0-inf, and Cmax were within the 80.00% to 125.00% range. The intra-subject CV% was low at 4% to 5%.

Nonparametric Statistical Comparison of Plasma R-Warfarin Tmax Following ACH-0144471 TID + Warfarin Versus Warfarin Alone (Part 1) (Pharmacokinetic Population)

	Warfarin Alone	ACH-0144471 TID + Warfarin	Difference ACH-0144471 TID + Warfarin - Warfarin Alone		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	4.00	4.00	0.00	0.0000, 1.0085	0.0703

Warfarin Alone: 200 mg ACH-0144471 administered orally TID on Days 1-11 with 25 mg warfarin coadministered on Day 5 (test)
ACH-0144471 TID + Warfarin: 25 mg warfarin administered orally on Day 1 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.1.1.7
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Based on the nonparametric statistical comparison, the difference in plasma R-warfarin Tmax between the coadministration of warfarin with ACH-0144471 (test) and the administration of warfarin alone (reference) was not statistically significant (p-value > 0.05).

Part 1 (Plasma S-Warfarin)

The statistical comparisons of plasma R-warfarin PK parameters AUC0-t, AUC0-inf, and Cmax and the non-parametric comparisons of R-warfarin Tmax are summarized in the following tables.

Statistical Comparisons of Plasma S-Warfarin Pharmacokinetic Parameters Following ACH-0144471 TID + Warfarin Versus Warfarin Alone (Part 1) (Pharmacokinetic Population)

	ACH-0144471 TID + Warfarin (Test)		Warfarin Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	48070	12	42340	12	113.54	110.98 - 116.16	3.11
AUC0-inf (ng*hr/mL)	49990	12	43870	12	113.93	111.25 - 116.68	3.25
Cmax (ng/mL)	1248	12	1194	12	104.52	99.06 - 110.28	7.33

ACH-0144471 TID + Warfarin: 200 mg ACH-0144471 administered orally TID on Days 1-11 with 25 mg warfarin coadministered on Day 5 (test)
Warfarin Alone: 25 mg warfarin administered orally on Day 1 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.1.2.6
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Based on GMR values, peak and extent of exposure to S-warfarin were slightly higher following the coadministration of warfarin with ACH-0144471 compared to the administration of warfarin alone (differences of approximately 5% to 14%). The 90% CIs of GMR for peak and extent of exposure were within the 80.00% to 125.00% range. The intra-subject CV% was low at 3% to 7%.

Nonparametric Statistical Comparison of Plasma S-Warfarin Tmax Following ACH-0144471 TID + Warfarin Versus Warfarin Alone (Part 1) (Pharmacokinetic Population)

	Warfarin Alone	ACH-0144471 TID + Warfarin	Difference ACH-0144471 TID + Warfarin - Warfarin Alone		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	4.00	4.00	1.00	-0.0005, 1.0085	0.1406

Warfarin Alone: 200 mg ACH-0144471 administered orally TID on Days 1-11 with 25 mg warfarin coadministered on Day 5 (test)
ACH-0144471 TID + Warfarin: 25 mg warfarin administered orally on Day 1 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.1.2.7
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Based on the nonparametric statistical comparison, the difference in plasma S-warfarin Tmax between the coadministration of warfarin with ACH-0144471 (test) and the administration of warfarin alone (reference) was not statistically significant (p-value > 0.05).

Part 1 (Plasma ACH-0144471)

The statistical comparisons of plasma ACH-0144471 PK parameters AUC0-8 and Cmax and the non-parametric comparisons of ACH-0144471 Tmax are summarized in the following tables.

Statistical Comparisons of Plasma ACH-0144471 Pharmacokinetic Parameters Following ACH-0144471 TID + Warfarin Versus ACH-0144471 TID (Part 1) (Pharmacokinetic Population)

	ACH-0144471 TID + Warfarin (Test)		ACH-0144471 TID (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-8 (ng*hr/mL)	1874	12	2255	12	83.11	78.93 - 87.51	7.04
Cmax (ng/mL)	435.1	12	533.9	12	81.49	72.21 - 91.97	16.61

ACH-0144471 TID + Warfarin: 200 mg ACH-0144471 administered orally TID on Days 5-11 with 25 mg warfarin coadministered on Day 5 (test)
ACH-0144471 TID: 200 mg ACH-0144471 administered orally TID on Days 1-4 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
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Based on GMR values, peak and extent of exposure to ACH-0144471 were approximately 19% and 17% lower, respectively, following the coadministration of ACH-0144471 with warfarin compared to the administration of ACH-0144471 alone. The 90% CIs of GMR for Cmax and AUC0-8 were outside the lower limit of the 80.00% to 125.00% range. The intra-subject CV% was low at 7 to 17%.

Nonparametric Statistical Comparison of Plasma ACH-0144471 Tmax Following ACH-0144471 TID + Warfarin Versus ACH-0144471 TID (Part 1) (Pharmacokinetic Population)

	ACH-0144471 TID	ACH-0144471 TID + Warfarin	Difference ACH-0144471 TID + Warfarin - ACH-0144471 TID		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	3.03	4.00	0.49	-0.2750, 1.0020	0.3804

ACH-0144471 TID: 200 mg ACH-0144471 administered orally TID on Days 5-11 with 25 mg warfarin coadministered on Day 5 (test)
ACH-0144471 TID + Warfarin: 200 mg ACH-0144471 administered orally TID on Days 1-4 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.1.3.6
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the difference in plasma ACH-0144471 Tmax between the coadministration of ACH-0144471 with warfarin (test) and the administration of ACH-0144471 alone (reference) was not statistically significant (p-value > 0.05).

Part 2 (Plasma Bupropion):

The statistical comparisons of plasma bupropion PK parameters AUC0-t, AUC0-inf, and Cmax and the non-parametric comparisons of bupropion Tmax are summarized in the following tables.

Statistical Comparisons of Plasma Bupropion Pharmacokinetic Parameters Following ACH-0144471 TID + Bupropion Versus Bupropion Alone (Part 2) (Pharmacokinetic Population)

	ACH-0144471 TID + Bupropion HCl (Test)		Bupropion HCl Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	804.3	16	722.0	16	111.40	106.10 - 116.97	7.88
AUC0-inf (ng*hr/mL)	830.3	16	743.7	16	111.65	106.47 - 117.07	7.66
Cmax (ng/mL)	130.4	16	124.0	16	105.13	93.22 - 118.56	19.58

ACH-0144471 TID + Bupropion HCl: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 100 mg bupropion HCl coadministered on Day 5 (test)
Bupropion HCl Alone: 100 mg bupropion HCl administered orally on Day 1 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.2.1.6
Program: /CA27858/sas_prg/pksas/adam_intext_statsmixed.sas 07MAY2020 15:14

Based on GMR values, peak and extent of exposure to bupropion were 5% to 12% higher following the coadministration of bupropion with ACH-0144471 compared to the administration of bupropion alone. The 90% CIs of GMR for Cmax, AUC0-t, and AUC0-inf were contained within the 80.00% to 125.00% range. The intra-subject CV% was low at 8% for AUCs and moderate at 20% for Cmax.

Nonparametric Statistical Comparison of Plasma Bupropion Tmax Following ACH-0144471 TID + Bupropion Versus Bupropion Alone (Part 2) (Pharmacokinetic Population)

	Bupropion Alone	ACH-0144471 TID + Bupropion	Difference ACH-0144471 TID + Bupropion - Bupropion Alone		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	1.49	3.00	1.00	0.5135, 1.2675	0.0008

Bupropion Alone: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 100 mg bupropion HCl coadministered on Day 5 (test)
ACH-0144471 TID + Bupropion: 100 mg bupropion HCl administered orally on Day 1 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.2.1.7
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the median difference of 1 hour in plasma bupropion Tmax between the coadministration of bupropion with ACH-0144471 (test) and administration of bupropion alone (reference) was statistically significant (p-value < 0.05). These results should be interpreted with caution due to the overlapping in the bupropion Tmax values between bupropion HCl alone (0.99 to 4.00 hours) and ACH-0144471 TID + bupropion HCl (1.50 to 5.00 hours).

Part 2 (Plasma Hydroxybupropion)

The statistical comparisons of plasma hydroxybupropion PK parameters AUC0-t, AUC0-inf, and Cmax and the non-parametric comparisons of hydroxybupropion Tmax are summarized in the following tables.

Statistical Comparisons of Plasma Hydroxybupropion Pharmacokinetic Parameters Following ACH-0144471 TID + Bupropion Versus Bupropion Alone (Part 2) (Pharmacokinetic Population)

	ACH-0144471 TID + Bupropion HCl (Test)		Bupropion HCl Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	8711	16	8998	16	96.80	92.12 - 101.72	8.01
AUC0-inf (ng*hr/mL)	9519	16	9765	16	97.48	92.07 - 103.21	9.23
Cmax (ng/mL)	219.5	16	237.0	16	92.61	87.38 - 98.16	9.41

ACH-0144471 TID + Bupropion HCl: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 100 mg bupropion HCl coadministered on Day 5 (test)
Bupropion HCl Alone: 100 mg bupropion HCl administered orally on Day 1 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.2.2.6
Program: /CA27858/sas_prg/pksas/adam_intext_statsmixed.sas 07MAY2020 15:14

Based on GMR values, peak and extent of exposure to hydroxybupropion were similar (3% to 7% lower) following coadministration of bupropion with ACH-0144471 compared to administration of bupropion alone. The 90% CIs of GMR for AUC0-t, AUC0-inf, and Cmax, were inside the 80.00% to 125.00% range. The intra-subject CV% was low at 8% to 9%.

Nonparametric Statistical Comparison of Plasma Hydroxybupropion Tmax Following ACH-0144471 TID + Bupropion Versus Bupropion Alone (Part 2) (Pharmacokinetic Population)

	Bupropion Alone	ACH-0144471 TID + Bupropion	Difference ACH-0144471 TID + Bupropion - Bupropion Alone		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	3.51	4.00	1.00	0.0075, 1.9985	0.0443

Bupropion Alone: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 100 mg bupropion HCl coadministered on Day 5 (test)
ACH-0144471 TID + Bupropion: 100 mg bupropion HCl administered orally on Day 1 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.2.2.7
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the median difference of 1 hour in plasma hydroxybupropion Tmax between the coadministration of bupropion with ACH-0144471 (test) and administration of bupropion alone (reference) was statistically significant (p-value < 0.05).

Taking in consideration the marginal significant p-value and the overlapping Tmax values between bupropion HCl alone and ACH-0144471 TID + bupropion HCl, the difference in Tmax might not be clinically significant.

Part 2 (Plasma ACH-0144471)

The statistical comparisons of plasma ACH-0144471 PK parameters AUC0-8 and Cmax and the non-parametric comparisons of ACH-0144471 Tmax are summarized in the following tables.

Statistical Comparisons of Plasma ACH-0144471 Pharmacokinetic Parameters Following ACH-0144471 TID + Bupropion Versus ACH-0144471 TID (Part 2) (Pharmacokinetic Population)

	ACH-0144471 TID + Bupropion HCl (Test)		ACH-0144471 TID (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-8 (ng*hr/mL)	2199	16	2511	16	87.58	81.44 - 94.19	11.78
Cmax (ng/mL)	544.5	16	630.0	16	86.43	74.31 - 100.52	24.73

ACH-0144471 TID + Bupropion HCl: 200 mg ACH-0144471 administered orally TID on Days 5-8 with 100 mg Bupropion HCl coadministered on Day 5 (test)
ACH-0144471 TID: 200 mg ACH-0144471 administered orally TID on Days 1-4 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.2.3.5
Program: /CA27858/sas_prg/pksas/adam_intext_statsmixed.sas 07MAY2020 15:14

Based on GMR values, peak and extent of exposure to ACH-0144471 were approximately 12 to 14% lower following the coadministration of ACH-0144471 with bupropion compared to administration of ACH-0144471 alone. The 90% CI of the AUC0-8 GMR was within the 80.00% to 125.00% range; however, the lower bound of the 90% CI of the Cmax GMR was outside the range. The intra-subject CV% was moderate at 12% for AUC0-8 and 25% for Cmax.

Nonparametric Statistical Comparison of Plasma ACH-0144471 Tmax Following ACH-0144471 TID + Bupropion Versus ACH-0144471 TID (Part 2) (Pharmacokinetic Population)

	ACH-0144471 TID	ACH-0144471 TID + Bupropion HCl	Difference ACH-0144471 TID + Bupropion HCl - ACH-0144471 TID		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	3.99	4.00	0.00	-0.4965, 0.5040	0.7532

ACH-0144471 TID: 200 mg ACH-0144471 administered orally TID on Days 5-8 with 100 mg Bupropion HCl coadministered on Day 5 (test)
ACH-0144471 TID + Bupropion HCl: 200 mg ACH-0144471 administered orally TID on Days 1-4 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.2.3.6
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the difference in plasma ACH-0144471 Tmax between the coadministration of ACH-0144471 with bupropion (test) and administration of ACH-0144471 alone (reference) was not statistically significant (p-value > 0.05).

Part 3 (Plasma EE):

The statistical comparisons of plasma EE PK parameters AUC0-t, AUC0-inf, and Cmax and the non-parametric comparisons of EE Tmax are summarized in the following tables.

Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following ACH-0144471 TID + Ethinyl Estradiol/Norethindrone Versus Ethinyl Estradiol/Norethindrone Alone (Part 3) (Pharmacokinetic Population)

	ACH-0144471 TID + Ethinyl Estradiol / Norethindrone (Test)		Ethinyl Estradiol / Norethindrone Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	859.9	22	664.0	24	129.50	105.92 - 158.33	40.88
AUC0-inf (ng*hr/mL)	1109	21	893.5	23	124.13	102.49 - 150.33	37.54
Cmax (ng/mL)	65.12	22	60.94	24	106.86	99.87 - 114.35	13.16

ACH-0144471 TID + Ethinyl Estradiol / Norethindrone: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 0.035 mg ethinyl estradiol / 1 mg norethindrone coadministered on Day 5 (test)
Ethinyl Estradiol / Norethindrone Alone: 0.035 mg ethinyl estradiol / 1 mg norethindrone administered orally on Day 1 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.3.1.6
Program: /CA27858/sas_prg/pksas/adam_intext_statsmixed.sas 07MAY2020 15:14

Based on GMR values, peak (Cmax) and extent (AUC0-t and AUC0-inf) of exposures to EE were approximately 7% and 24% - 30%, respectively, higher following coadministration of EE/NET with ACH-0144471 compared to administration of EE/NET alone, while the 90% CI of the Cmax GMR was within the 80.00% to 125.00% range, and those for AUCs were outside the range. The intra-subject CV% was moderate at 13% for Cmax and 38% or 41% for AUCs.

Nonparametric Statistical Comparison of Plasma Ethinyl Estradiol Tmax Following ACH-0144471 TID + Ethinyl Estradiol/Norethindrone Versus Ethinyl Estradiol/Norethindrone Alone (Part 3) (Pharmacokinetic Population)

	Ethinyl Estradiol / Norethindrone Alone	ACH-0144471 TID + Ethinyl Estradiol / Norethindrone	Difference ACH-0144471 TID + Ethinyl Estradiol / Norethindrone - Ethinyl Estradiol / Norethindrone Alone		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	2.76	4.09	0.50	0.0250, 1.1820	0.0553

Ethinyl Estradiol / Norethindrone Alone: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 0.035 mg ethinyl estradiol / 1 mg norethindrone coadministered on Day 5 (test)
ACH-0144471 TID + Ethinyl Estradiol / Norethindrone: 0.035 mg ethinyl estradiol / 1 mg norethindrone administered orally on Day 1 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.3.1.7
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the median difference of 0.5 hour in plasma EE Tmax between the coadministration of EE/NET with ACH-0144471 (test) and administration of EE/NET alone (reference) was not statistically significant (p-value > 0.05).

Part 3 (Plasma NET)

The statistical comparisons of plasma NET PK parameters AUC0-t, AUC0-inf, and Cmax and the non-parametric comparisons of NET Tmax are summarized in the following tables.

Statistical Comparisons of Plasma Norethindrone Pharmacokinetic Parameters Following ACH-0144471 TID + Ethinyl Estradiol/Norethindrone Versus Ethinyl Estradiol/Norethindrone Alone (Part 3) (Pharmacokinetic Population)

	ACH-0144471 TID + Ethinyl Estradiol / Norethindrone (Test)		Ethinyl Estradiol / Norethindrone Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-t (ng*hr/mL)	53920	22	47160	24	114.32	102.16 - 127.93	22.05
AUC0-inf (ng*hr/mL)	55790	22	49020	24	113.81	102.02 - 126.95	21.42
Cmax (ng/mL)	8015	22	7068	24	113.40	98.27 - 130.86	28.44

ACH-0144471 TID + Ethinyl Estradiol / Norethindrone: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 0.035 mg ethinyl estradiol / 1 mg norethindrone coadministered on Day 5 (test)
Ethinyl Estradiol / Norethindrone Alone: 0.035 mg ethinyl estradiol / 1 mg norethindrone administered orally on Day 1 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.3.2.6
Program: /CA27858/sas_prg/pksas/adam_intext_statsmixed.sas 07MAY2020 15:14

Based on GMR values, peak (Cmax) and extent (AUC0-t and AUC0-inf) of exposure to NET were 13% to 14% higher following the coadministration of EE/NET with ACH-0144471 compared to administration of EE/NET alone. The 90% CIs of GMR for AUCs and Cmax fell outside the 80.00% to 125.00% range. The intra-subject CV% was moderate at 21% to 28%.

Nonparametric Statistical Comparison of Plasma Norethindrone Tmax Following ACH-0144471 TID + Ethinyl Estradiol/Norethindrone Versus Ethinyl Estradiol/Norethindrone Alone (Part 3) (Pharmacokinetic Population)

	Ethinyl Estradiol / Norethindrone Alone	ACH-0144471 TID + Ethinyl Estradiol / Norethindrone	Difference ACH-0144471 TID + Ethinyl Estradiol / Norethindrone - Ethinyl Estradiol / Norethindrone Alone		
Parameter	**Median**	**Median**	**Median Difference**	**Minimum, Maximum**	**p-value**
Tmax	2.25	3.08	0.83	0.3620, 1.3150	0.0034

Ethinyl Estradiol / Norethindrone Alone: 200 mg ACH-0144471 administered orally TID on Days 1-8 with 0.035 mg ethinyl estradiol / 1 mg norethindrone coadministered on Day 5 (test)
ACH-0144471 TID + Ethinyl Estradiol / Norethindrone: 0.035 mg ethinyl estradiol / 1 mg norethindrone administered orally on Day 1 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.3.2.7
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the difference in plasma NET Tmax between the coadministration of EE/NET with ACH-0144471 (test) and administration of EE/NET alone (reference) was statistically significant (p-value < 0.05).

Part 3 (Plasma ACH-0144471)

The statistical comparisons of plasma ACH-0144471 PK parameters AUC0-8 and Cmax and the non-parametric comparisons of ACH-0144471 Tmax are summarized in the following tables.

Statistical Comparisons of Plasma ACH-0144471 Pharmacokinetic Parameters Following ACH-0144471 TID + Ethinyl Estradiol/Norethindrone Versus ACH-0144471 TID (Part 3) (Pharmacokinetic Population)

	ACH-0144471 TID + Ethinyl Estradiol / Norethindrone (Test)		ACH-0144471 TID (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC0-8 (ng*hr/mL)	2977	22	3607	22	82.54	74.75 - 91.15	19.30
Cmax (ng/mL)	694.9	22	806.3	22	86.19	76.14 - 97.57	24.25

ACH-0144471 TID + Ethinyl Estradiol / Norethindrone: 200 mg ACH-0144471 administered orally TID on Days 5-8 with 0.035 mg ethinyl estradiol / 1 mg norethindrone coadministered on Day 5 coadministered on Day 5 (test)
ACH-0144471 TID: 200 mg ACH-0144471 administered orally TID on Days 1-4 (reference)
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV% was calculated as 100*square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.
Source: Table 14.2.3.3.5
Program: /CA27858/sas_prg/pksas/adam_intext_statsmixed.sas 07MAY2020 15:14

Based on GMR values, peak and extent of exposure to ACH-0144471 were approximately 14% to 17% lower following the coadministration of ACH-0144471 with EE/NET compared to administration of ACH-0144471 alone. The 90% CIs of GMR for AUC0-8 and Cmax were outside the 80.00% to 125.00% range. The intra-subject CV% was moderate at 19% for AUC0-8 and 24% for Cmax.

Nonparametric Statistical Comparison of Plasma ACH-0144471 Tmax Following ACH-0144471 TID + Ethinyl Estradiol/Norethindrone Versus ACH-0144471 TID (Part 3) (Pharmacokinetic Population)

	ACH-0144471 TID	ACH-0144471 TID + Ethinyl Estradiol / Norethindrone	Difference ACH-0144471 TID + Ethinyl Estradiol / Norethindrone - ACH-0144471 TID		
Parameter	Median	Median	Median Difference	Minimum, Maximum	p-value
Tmax	3.00	4.13	0.69	0.2085, 1.5730	0.0083

ACH-0144471 TID: 200 mg ACH-0144471 administered orally TID on Days 5-8 with 0.035 mg ethinyl estradiol / 1 mg norethindrone coadministered on Day 5 coadministered on Day 5 (test)
ACH-0144471 TID + Ethinyl Estradiol / Norethindrone: 200 mg ACH-0144471 administered orally TID on Days 1-4 (reference)
The median is estimated using the Hodges-Lehmann method. The 90% confidence interval is constructed using Walsh Averages and appropriate quantile of the Wilcoxon Signed Ranks test statistic.
Source: Table 14.2.3.3.6
Program: /CA27858/sas_prg/pksas/adam_intext_nonpar.sas 26MAY2020 16:36

Based on the nonparametric statistical comparison, the median difference of 0.69 hours in plasma ACH-0144471 Tmax between the coadministration of ACH-0144471 with EE/NET (test) and administration of ACH-0144471 alone (reference) was statistically significant (p-value < 0.05).

Analysis of Pharmacodynamics (Part 1)

The statistical comparisons of blood INR measurements PD parameters are summarized in the following table.

Statistical Comparisons of Blood INR Pharmacodynamic Parameters: ACH-0144471 TID + Warfarin Versus Warfarin Alone (Pharmacodynamic Population) – Part 1

	ACH-0144471 TID + Warfarin (Test)		Warfarin Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
INR AUC0-168	217.72	12	227.96	12	95.51	94.26 - 96.77	1.79
INRmax	1.73	12	1.95	12	88.64	85.92 - 91.45	4.26

Warfarin Alone: 25 mg warfarin administered orally on Day 1
ACH-0144471 TID + Warfarin: 200 mg ACH-0144471 administered orally TID on Days 1-11 with 25 mg warfarin coadministered on Day 5
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100*(test/reference)
Intra-subject CV (CV%) = 100*(square root (exp[MSE]-1))
Source: Table 14.2.1.7.5
Program: /CA27858/sas_prg/pksas/pd/adam_intext_statsmixed_pd.sas 09APR2020 10:40

The statistical analysis of blood INR measurements indicated that the values of INR AUC0-168 and INRmax were slightly lower (by 4 to 11%) following coadministration of ACH-0144471 with warfarin compared to administration of warfarin alone. The 90% CIs of GMR for AUC0-168 and INRmax fell within the 80.00% to 125.00% range. The intra-subject CV% was low at approximately 2% for INR AUC0-168 and 4% for INRmax.

Safety Results:

There were no deaths in this study. One (1) subject was discontinued from Part 3 of the study due to an serious adverse events (SAE) of macular hole and another subject in Part 3 was discontinued due to a treatment-emergent adverse event (TEAE) of increased blood pressure. Both events were considered unrelated to study treatment. Overall, there was a greater percentage of subjects with AEs in Part 3 of this study (71%), with constipation, headache, and somnolence being the most common AEs. The PI considered these TEAEs related to ACH-0144471. Parts 1 and 2 of the study had significantly lower percentages of subjects with AEs (8% and 25%, respectively), and all were considered unlikely or unrelated to ACH-0144471. The majority of AEs in all study parts were mild in severity

There were no remarkable findings in the remaining safety assessments for vital signs, ECGs, laboratory values or physical examinations.

Conclusions:

Pharmacokinetics

Part 1:

- The extent (AUC0-t and AUC0-inf) and peak (Cmax) exposures to R- and S-warfarin following coadministration of warfarin with ACH-0144471 were similar to that after administration of warfarin alone when evaluated using 90% CI of geometric means test (< 6% and 14% difference in R- and S-warfarin exposure, respectively). The times to reach peak R- and S-warfarin exposure (Tmax) were not significantly different between the administration of warfarin alone and coadministered with ACH-0144471.
- A single dose of warfarin decreased plasma ACH-0144471 exposure as measured by AUC0-8 and Cmax by 17% and 19%, respectively, when administered while subjects were receiving multiple doses of ACH-0144471. Tmax for ACH-0144471 was not significantly different between the administration of ACH-0144471 alone and coadministered with warfarin.

Part 2:

- The extent (AUC0-t and AUC0-inf) and peak (Cmax) exposures to bupropion following coadministration with ACH-0144471 were similar to that after administration of bupropion alone when evaluated using 90% CI of geometric means test (with relatively small increases of ~12% and ~5%, respectively). The extent and peak exposures to hydroxybupropion following coadministration with ACH-0144471 were similar to that after administration of bupropion alone with small decreases of ~3% and ~7%, respectively.
- A single dose of bupropion decreased plasma ACH-0144471 exposure (AUC0-8 and Cmax) by approximately 12% to 14%, respectively, when administered while subjects were receiving multiple doses of ACH-0144471. Tmax for ACH-0144471 was not statistically different between the administration of ACH-0144471 alone and coadministered with bupropion.

Part 3:

- Administration of ACH-0144471 TID with EE/NET increased the exposure of both EE (by 7% to 30% for Cmax and AUCs, respectively) and NET (by 13% to 14%, for Cmax and AUCs, respectively) compared to dosing of EE/NET alone when evaluated using 90% CI of geometric means test. Tmax for EE was not significantly different between the administration of EE/NET alone and coadministered with ACH-0144471. However, Tmax for NET was statistically different between the administration of EE/NET alone (Tmax = 2.25 hours) and coadministered with ACH-0144471 (Tmax = 3.08 hours), which may not be clinically significant.
- A single dose of EE/NET decreased plasma ACH-0144471 exposure (AUC0-8 and Cmax) by approximately 17% and 14%, respectively, when administered while subjects were receiving multiple doses of ACH-0144471.

Pharmacodynamics

Part 1:

- Administration of warfarin after ACH-0144471 TID dosing had no effect on the pharmacodynamics (INR AUC0-168 and INRmax) of warfarin compared to dosing warfarin alone.

Safety:

- Multiple oral doses of ACH-0144471, when coadministered with single doses of warfarin, bupropion hydrochloride, and ethinyl estradiol/norethindrone, appeared to be safe and generally well tolerated by the healthy subjects in this study.

Date of Report: 04 June 2020