Bioequivalence and clinical implications of generic and brand bupropion

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U01FD004899

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DukeHealth

Bioequivalence and clinical effects of generic and brand bupropion

- 4th most prescribed antidepressant in the US (2007), >20M prescriptions (all forms)[1]
- Antidepressant bupropion available in immediate release (IR), twice daily (SL), daily (extended-release, XL) forms
- Generic IR, SL and 150mg XL bupropion have established bioequivalence
- Generic 300mg XL approved based on extrapolating data from 150mg XL products (Because of concerns regarding risk of seizure with high doses of bupropion[2])
- First 300mg XL generic approved (Budeprion, 2006)
- Beginning 2007, patient complaints (clinical ineffectiveness, new/worse side effects) about Budeprion, then other generics

[1] Wikipedia, 2013

[2] Woodcock J: Withdrawal of generic budeprion for nonbioequivalence. N Engl J Med 2012;367:2463-5

Bioequivalence and clinical effects of generic and brand bupropion

- FDA (10/3/2012):

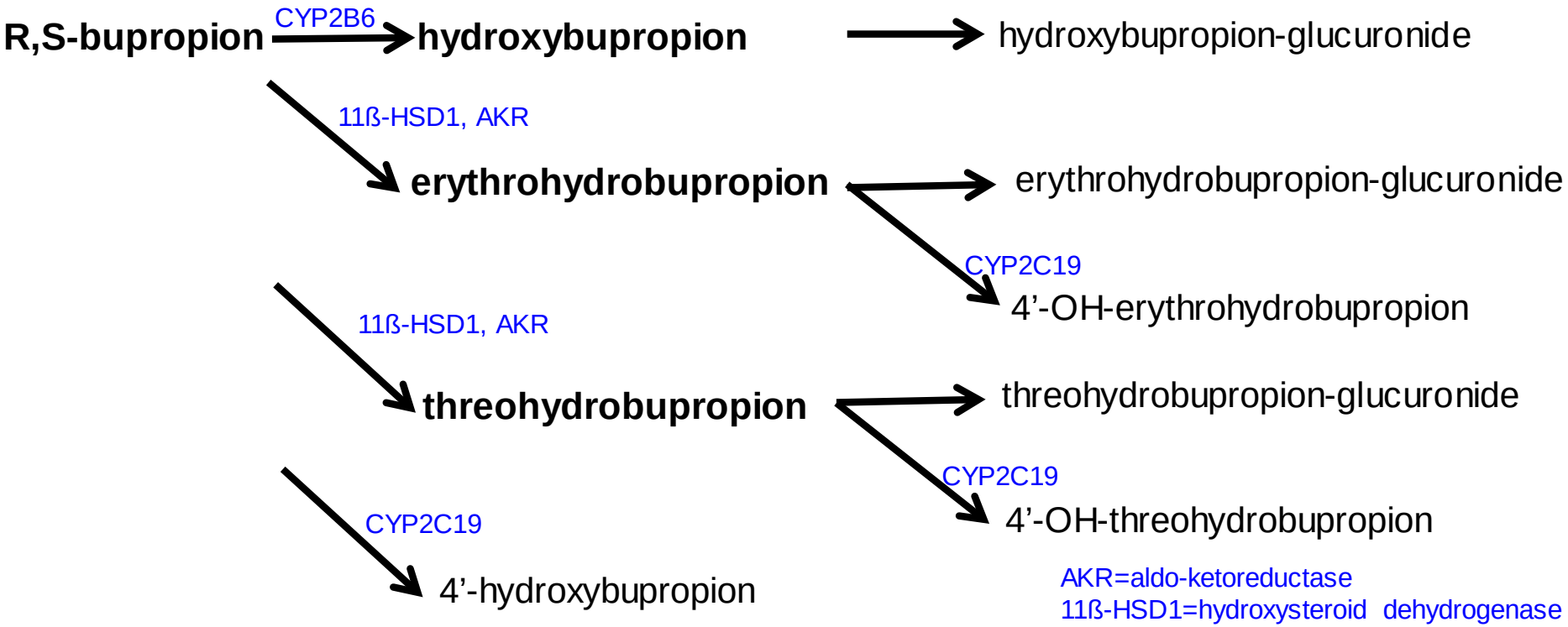
"FDA considers generic bupropion XL 300mg (Teva) bioequivalent and therapeutically equivalent to Wellbutrin XL 300mg. Although there are small differences in the pharmacokinetic profiles of these two formulations, they are not outside established boundaries for equivalence nor are they different from other bupropion products known to be effective."

"Recurrent nature of major depressive disorder offers a scientifically reasonable explanation for the reports of lack of efficacy following a switch to a generic product."

https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm153270.htm

Bupropion Disposition

- Extensively metabolized (<1% eliminated unchanged)
- Metabolites eliminated mostly in urine (87%) and feces (10%)
- Metabolized to hydroxybupropion (active metabolite) by CYP2B6; erythrohydrobupropion & threohydrobupropion (non-CYP)
- Metabolite exposure considerably higher than parent drug
- Bupropion is racemic; bupropion disposition is stereoselective



Bioequivalence of generic and brand bupropion

Perspective

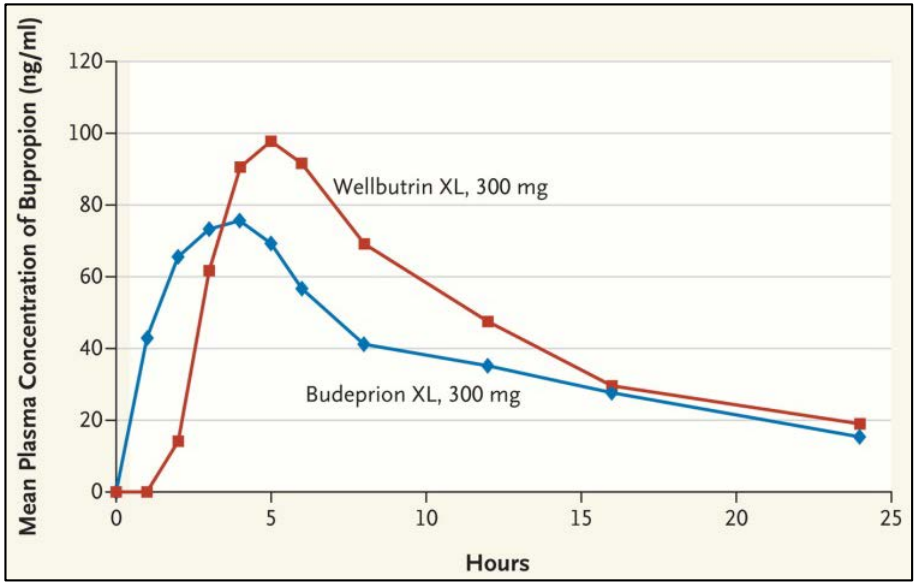
Withdrawal of Generic Budeprion for Nonbioequivalence

Janet Woodcock, M.D., Mansoor Khan, R.Ph., Ph.D., and Lawrence X. Yu, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2012;367:2463-5

- FDA sponsored single-dose bioequivalence crossover: 300mg Budeprion XL vs Wellbutrin XL in 24 healthy adult volunteers (complete August, 2012)
- Budeprion XL failed bioequivalence
  - AUC mean only 86% of Wellbutrin XL (90%CI 77-96%)
  - C_{max} mean only 75% (65-87%) of Wellbutrin XL
  - Hydroxybupropion C_{max} also failed
- Budeprion XL withdrawn 2012
- Cast doubt on entire generic bupropion market, which shrank precipitously
- Undermined confidence in generic drug approvals in general
- No bioequivalence or clinical equivalence data on any other 300mg XL generic (2013)



Bioequivalence generic bupropion

RFA-FD-13-021 Bioequivalence of Generic Bupropion (U01) (April 2, 2013)

1. Demonstrate bioequivalence between generic and brand bupropion HCl modified release products with different release patterns at steady state in patients
2. Evaluate whether patients can perceive difference in release pattern and experience lack of efficacy or increased adverse events after switch between each treatment
3. Outcome will help address concerns on quality, bioequivalence, and therapeutic equivalence of bupropion hydrochloride modified release generic products

Specific Aims

Bioequivalence and clinical effects of generic and brand bupropion - U01FD004899

1. Determine bioequivalence between brand and generic bupropion 300mg XL products (and between generic products) at steady state in patients with major depressive disorder
2. Compare patients' clinical response to each bupropion 300mg XL product, using objective, well-validated measures of depression response and side effects.
3. Compare patient perceptions of clinical differences (release patterns, antidepressant effectiveness, adverse events) between all bupropion 300mg XL products (brand vs generics, and between generics), using innovative methods for assessing patient perspectives

Clinical protocol

- Prospective, randomized, double-blinded, crossover
- Pts with major depressive disorder, on bupropion HCl 300mg XL (brand or generic) ≥4 mo
- 75 subjects (target, 60 evaluable)
- Total 28 week study
  - 4-wk lead-in (on own bupropion product; overencapsulated)
  - four 6-wk randomized cross-over phases on each of 4 bupropion study drugs
- Study drugs: (overencapsulated to ensure blinding)
  Brand: Valeant (formerly GSK Wellbutrin)
  Generic: Mylan, Watson, Par/Anchen
- Subjects not informed when switched, to minimize bias and expectancy
- Adherence monitoring (pill counts, MEMS cap)

Clinical protocol

Evaluations:

- Steady-state PK (plasma and urine, 24 hr sampling, day 10-day 20 window)
- Standard structured clinical evaluations (q3 wk in-person)
  - Depression (Montgomery-Asberg Depression Rating Scale; MADRS)
  - Drug side-effects (Antidepressant Side-Effect Checklist)
- Subjects' daily reports of side effects and symptoms using smart phone-based Ecological Daily Assessments (EDA, 13 item):
  - depressive symptoms; 5 items from MADRS (excluding suicide and depression)
  - 6 most common self-reported bupropion side effects (dry mouth, insomnia, headache, nausea, agitation, sweating)
- Patient retrospective evaluation of drug products

Clinical protocol

Inclusion Criteria

- Adult outpatients age 18-75 yr
- Major depressive disorder, partial or full remission for ≥4 mo, confirmed by Structured Clinical Interview for DSM Axis I Disorders (SCID)
- Currently on bupropion HCl 300mg XL qd (brand or generic) for minimum of 4 mo

Exclusion Criteria

- Remission from depression not clearly attributed to bupropion treatment
- Current severe side effects attributable to bupropion
- Poor adherence to bupropion treatment per patient self-report and history of refill persistence
- History of active seizure disorder, or seizure treatment within past year
- History of significant hepatic or renal disease, based on physician assessment
- Currently taking drugs or natural products known to influence CYP2B6 activity
- Currently taking drugs for hepatitis C or multiple sclerosis, due to ability to cause depression
- Dementia or other significant cognitive impairment, per diagnosis or investigator assessment
- Lifetime diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, delusional disorder, or current psychotic symptoms diagnosed by SCID
- Abuse of or dependence on alcohol or other substances within the past 6 mo as determined by SCID, and confirmed by study physician interview
- Current suicidal ideation

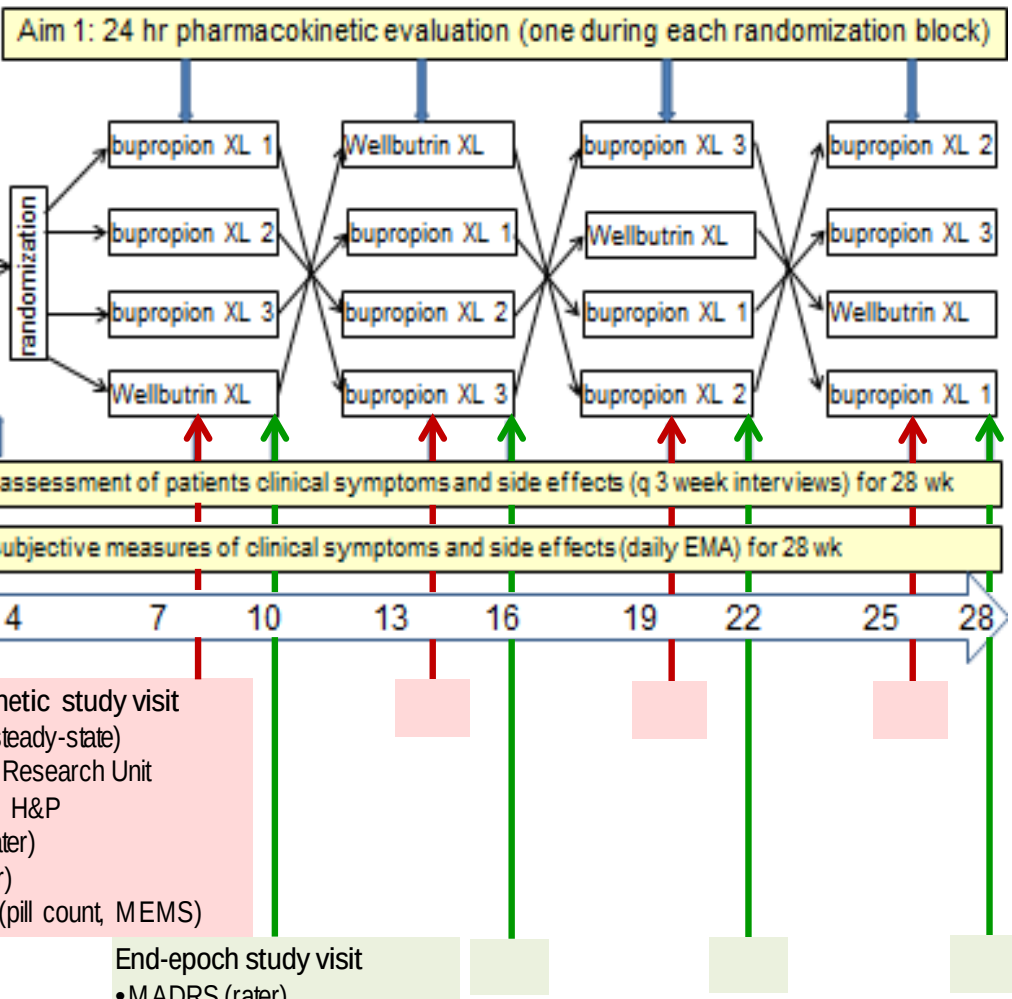
Clinical protocol

- Structured Clinical Interview for DSM Axis I Disorders (SCID)
- Montgomery-Asberg Depression Rating Scale (10 item MADRS)
- Modified Antidepressant Side-Effect Checklist (6 item, ASEC)
- Mini Mental State Exam
- Psychiatrist assessment

Recruit, screen

enroll

Lead-in (4 weeks)
Subjects' home bupropion product; over-encapsulated
Adherence monitoring (MEMS Cap)
Ecological daily assessment (EDA) via smart phone:
- mood assessment
- side effects rating
- daily dosing reminder



Ecological daily assessment (EDA) via smart phone:
- mood assessment
- side effects
- daily dosing reminder

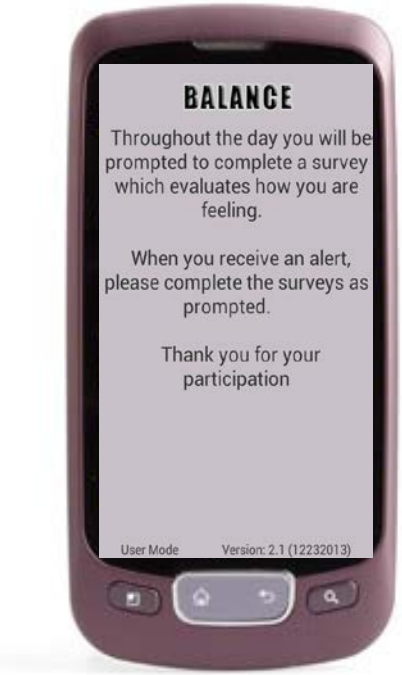
Pharmacokinetic study visit
Day 10-20 (steady-state)
24hr Clinical Research Unit
- Abbreviated H&P
- MADRS (rater)
- ASEC (rater)
- Adherence (pill count, MEMS)

End-epoch study visit
- MADRS (rater)
- ASEC (rater)
- Adherence (pill count, MEMS)
- Randomized double-blinded 6 wk supply OET study drug

Ecological daily assessment (EDA) via smart phone

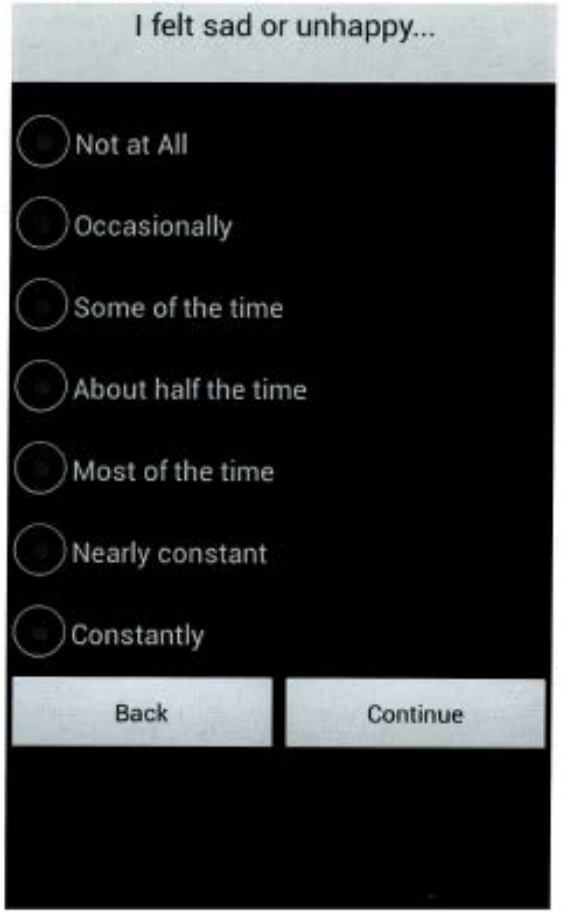
E-technology based assessments may be able to capture more subtle differences between medications

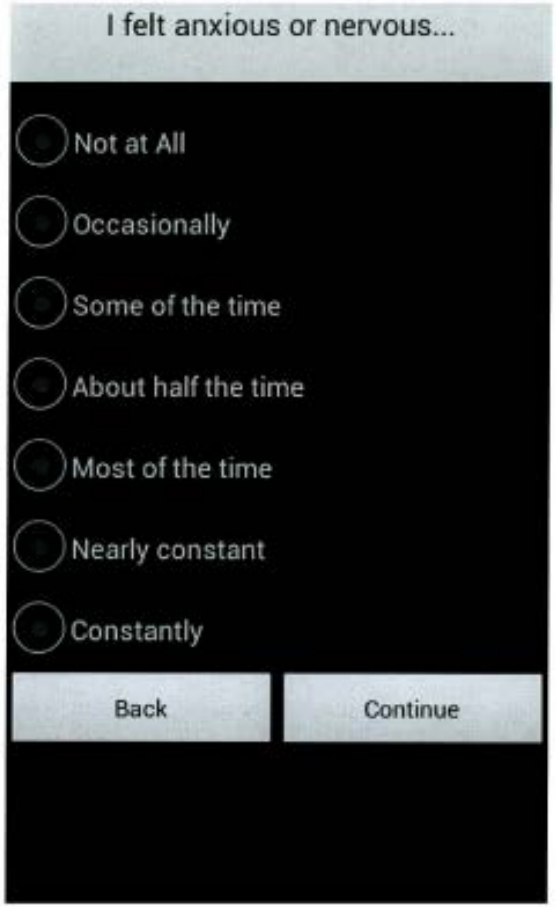
- Differences may be more reflected by side effects rather than by depression
- Differences may be difficult to detect using traditional assessments of depression (i.e. MADRS or Ham-D) and side effects, which assess symptoms retrospectively (“Over the last seven days…?”)
- Can e-technology help?

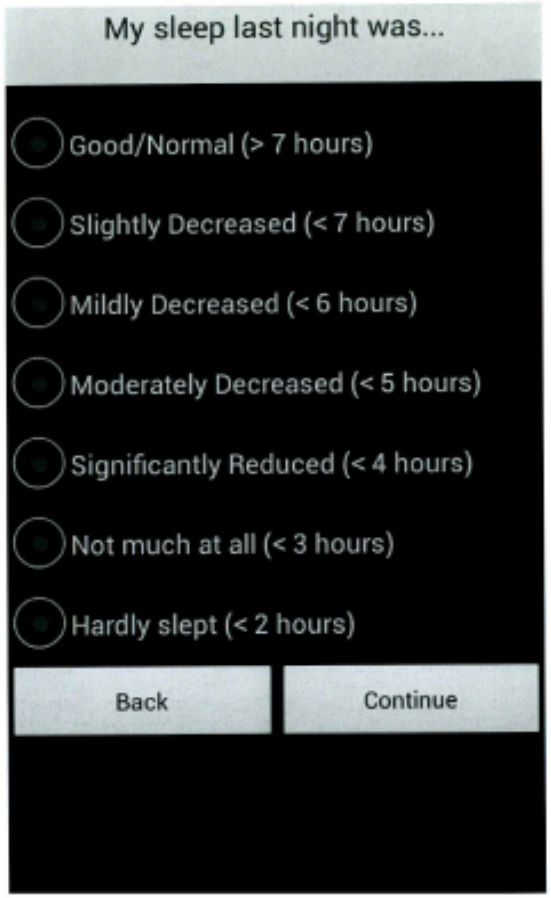


Ecological daily assessment (EDA) via smart phone

Assessments for depression



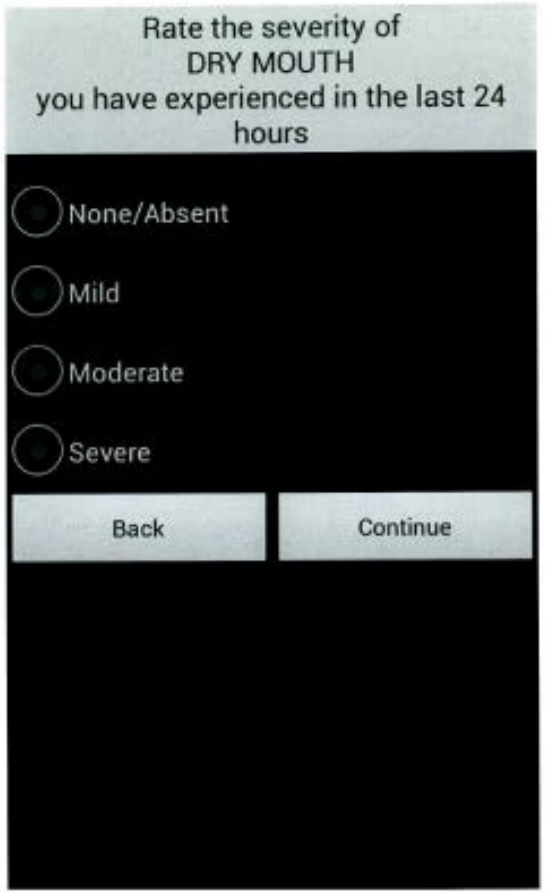




8 questions corresponding to MADRS items.

Ecological daily assessment (EDA) via smart phone

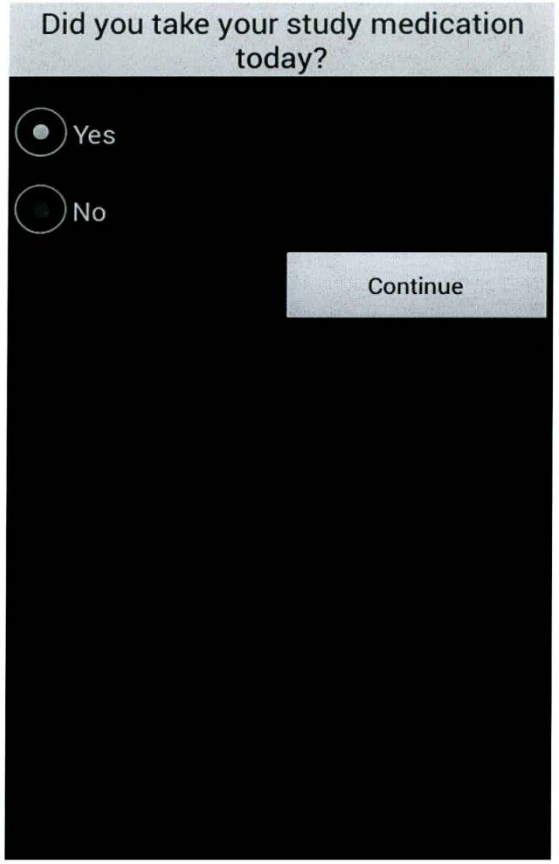
Assessments for side effects



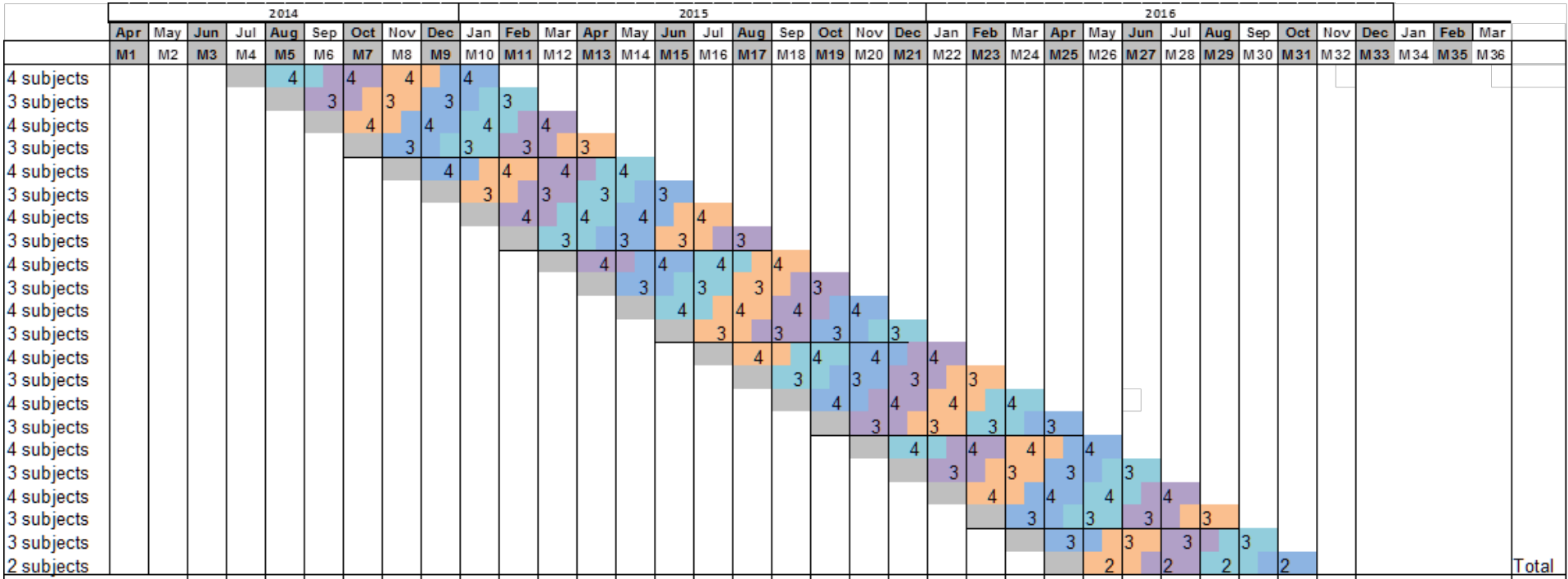
5 questions (plus insomnia item) assessing most common bupropion side effects

Ecological daily assessment (EDA) via smart phone

To improve treatment adherence



Timeline



Each column M1-M36 represents the month of the study; Each row is a cohort of 3-4 subjects
Grey box represents the drug product at the time of enrollment and entry into the study
Each color box is a different bupropion XL drug product
Each drug product is administered for 6 weeks
Pharmacokinetic sessions are performed during the day 10-20 window on each drug product
The number in each box shows the time of the PK session (2nd-3rd week) and the number of subjects

NOTES:
FDA Award notice Sep 15, 2013
Initial RIHSC approval Jan 9, 2014
WU IRB approval Apr 10, 2014
Mylan drug product unavialable until June 2014
Enrollment started July 2014
Projected date for study enrollment = Dec 2015
Projected date for 75 completed subjects = Oct 2016
Per protocol, only 60 evaluable subjects required, which may further accelerate this timeline

First subject enrolled 6/25/2014
Last subject enrolled 1/20/2016
Last subject completed 8/6/2016
Target: 60 evaluable
Actual: 70 evaluable
Exceeded timeline & enrollment

Clinical protocol

Primary outcome measure

C_{max} and AUC_{0-24} for racemic bupropion, hydroxybupropion, erythrohydrobupropion, threohydrobupropion

Bioequivalence calculated as difference (brand-generic) of log-transformed data, expressed as the geometric mean (antilog of the means of the logs)
Bioequivalence is considered when the 90% confidence interval is within 80%-125%

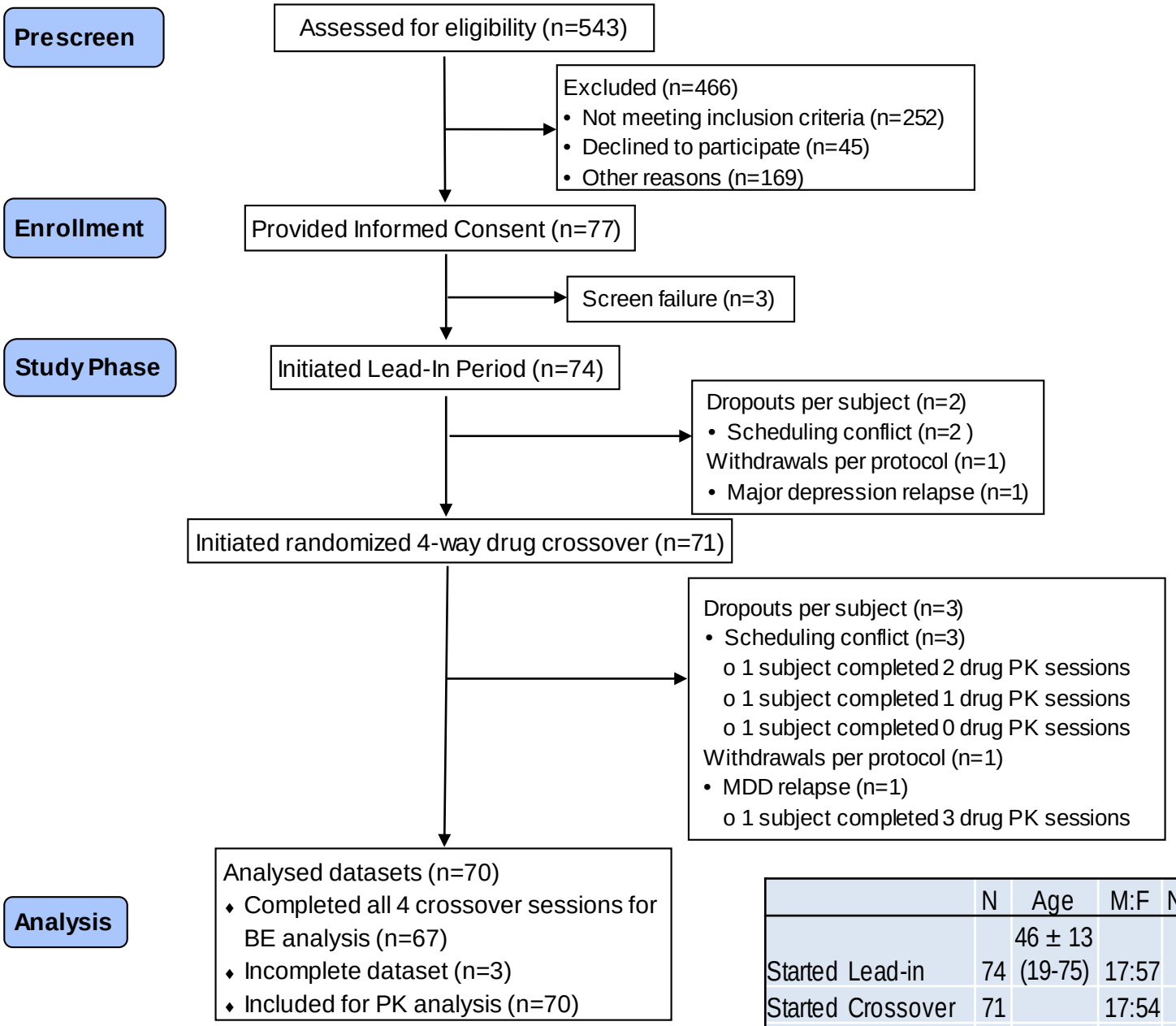
Additional pharmacokinetic/bioequivalence endpoints:

- T_{max} for racemic bupropion, hydroxybupropion, erythrohydrobupropion, threohydrobupropion

Secondary Endpoints:

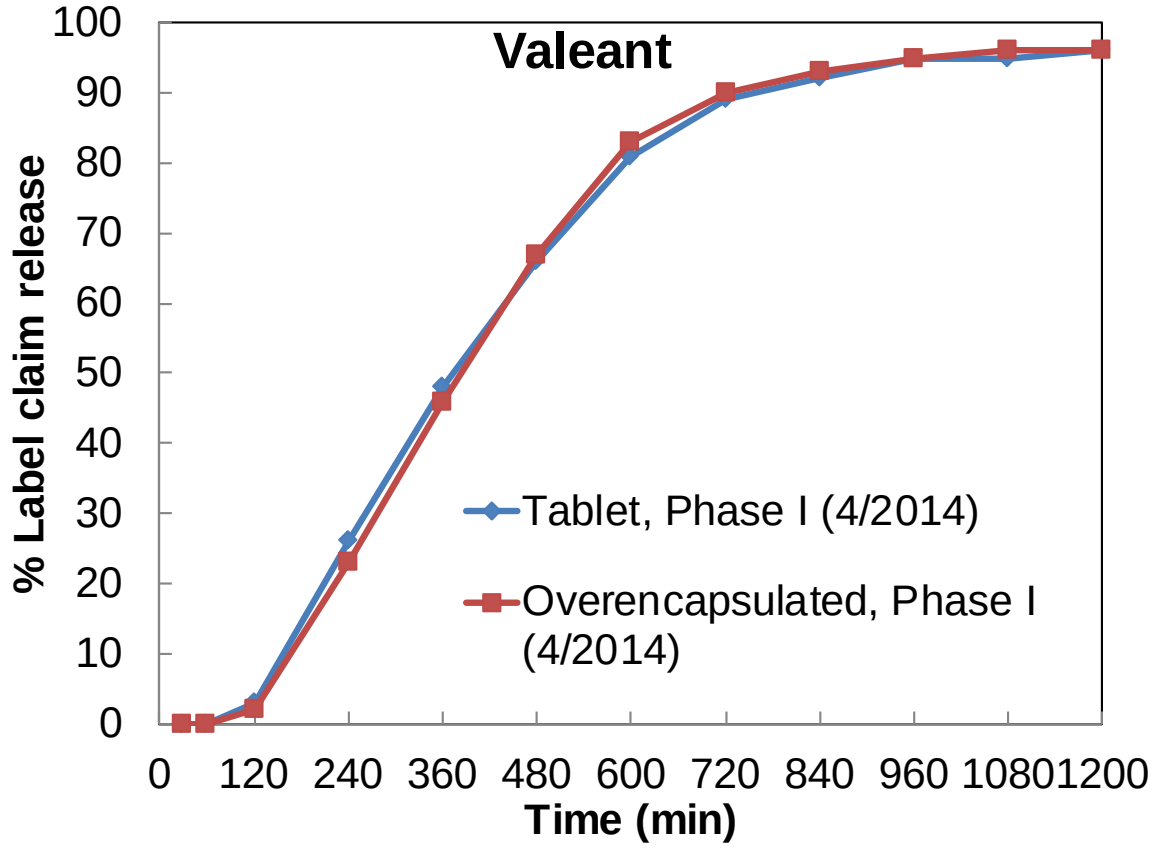
- Relapse of major depressive disorder
- Change in depression symptoms (periodic assessment and EDA)
- Change in side effects (periodic assessment and EDA)

Clinical protocol



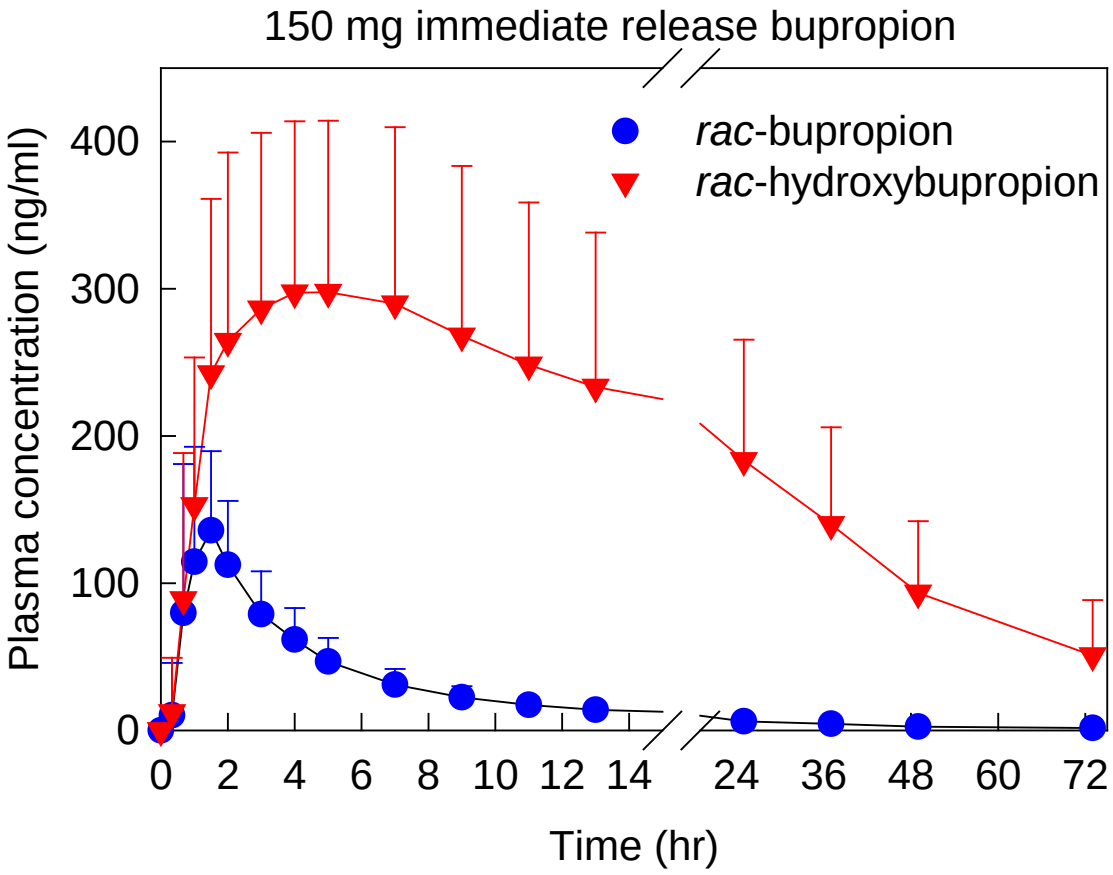
	N	Age	M:F	Non-Hisp	Hisp	Cauc	Afr Am	Asian
Started Lead-in	74	46 ± 13 (19-75)	17:57	72	2	68	5	1
Started Crossover	71		17:54	69	2	65	5	1
Completed all 4 PK	67		15:52	66	1	61	5	1

Bupropion preliminary assessment



- Overencapsulated drug assessed by formal dissolution testing (USP methods 38-NF31 and 37–NF32)
- Overencapsulation did not affect dissolution of any bupropion product used in the investigation

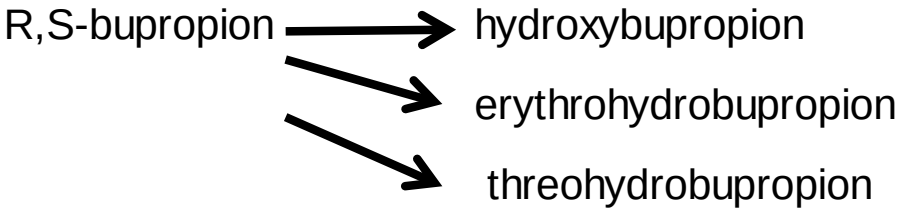
Bupropion preliminary assessment



Immediate-release bupropion HCl
- bupropion T_{max} 1-2 hr
- hydroxybupropion T_{max} 4-6 hr

Kharasch, CPT PMID: 29756345

Bupropion bioequivalence



Aim 1: Determine bioequivalence between brand and generic bupropion 300mg XL products (and between generic products) at steady state in patients with major depressive disorder

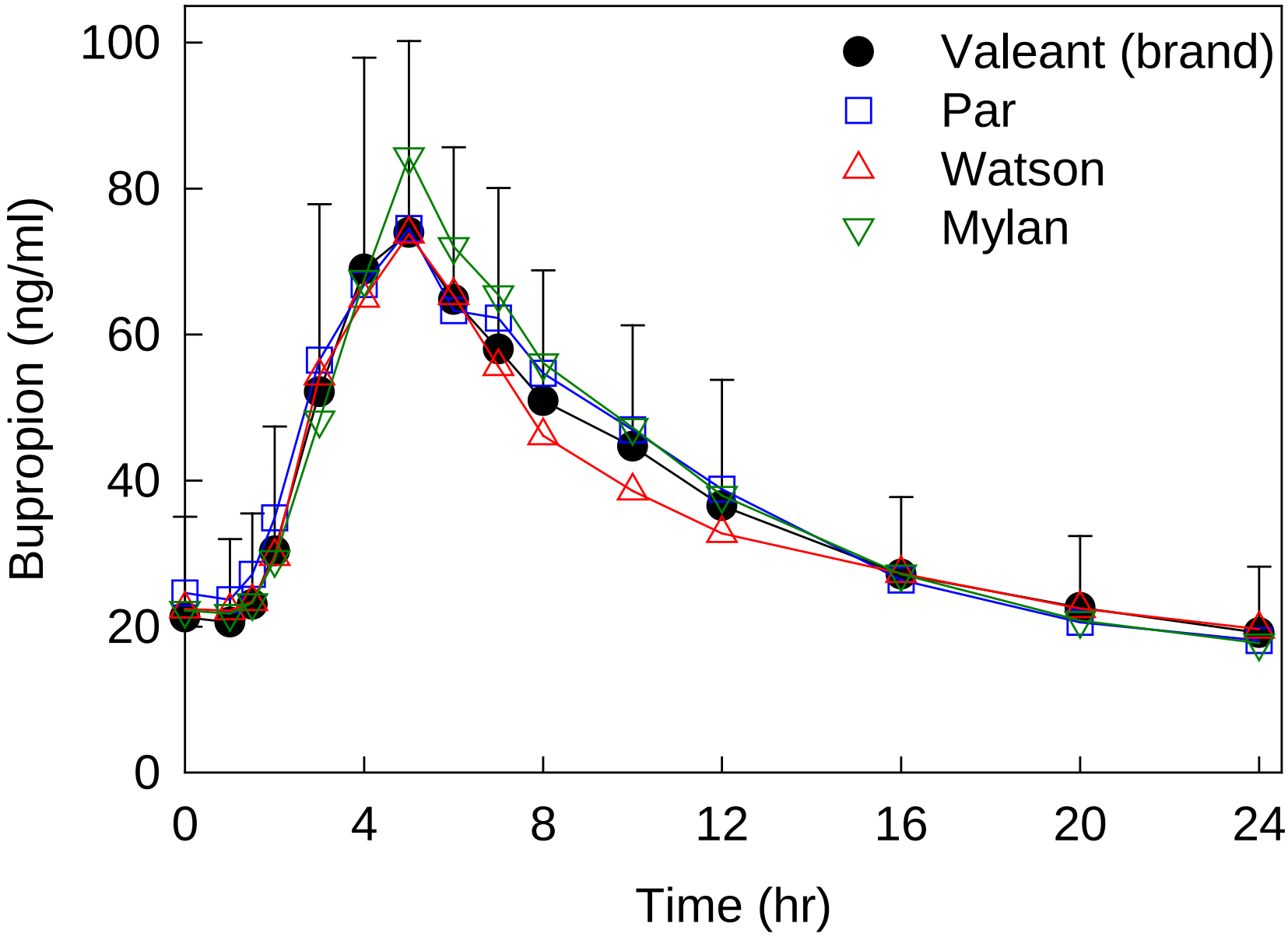
Primary outcomes:

rac-bupropion
rac-hydroxybupropion
rac-erythrohydrobupropion
rac-threohydrobupropion

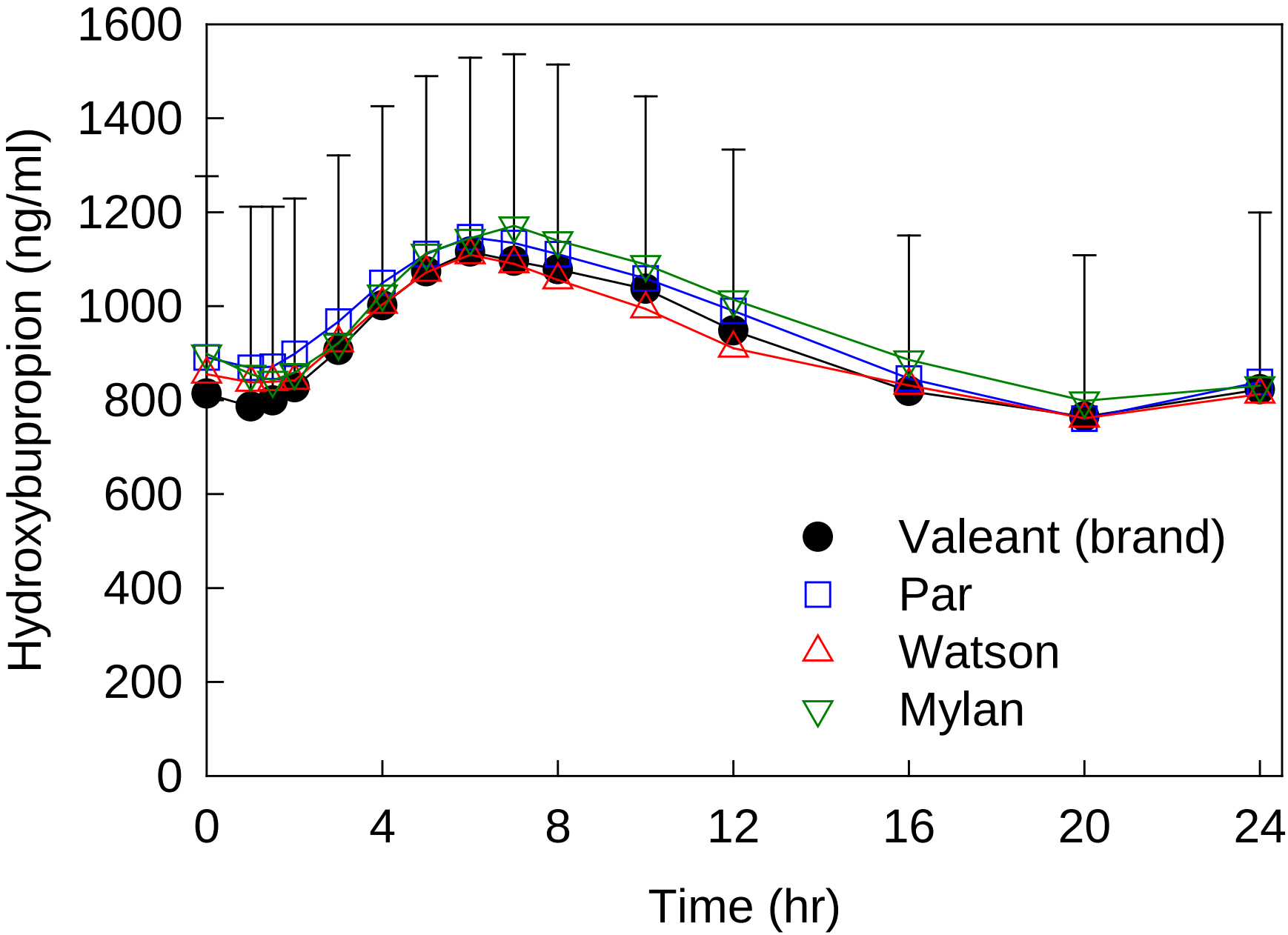
C_{max}
T_{max}
AUC_{0-24}

	AUClast (hr*µg/mL)	Cl/F (mL/kg/min)	AUC metabolite/ bupropion
R,S-bupropion	0.83 (0.71-1.04)	56 (38-76)	
rac-hydroxybupropion	21.2 (15.5-25.4)		24 (17-33)
rac-erythrohydrobupropion	2.1 (1.5-2.6)		2.3 (1.9-2.9)
rac-threohydrobupropion	9.4 (7.2-13.2)		11 (9-15)

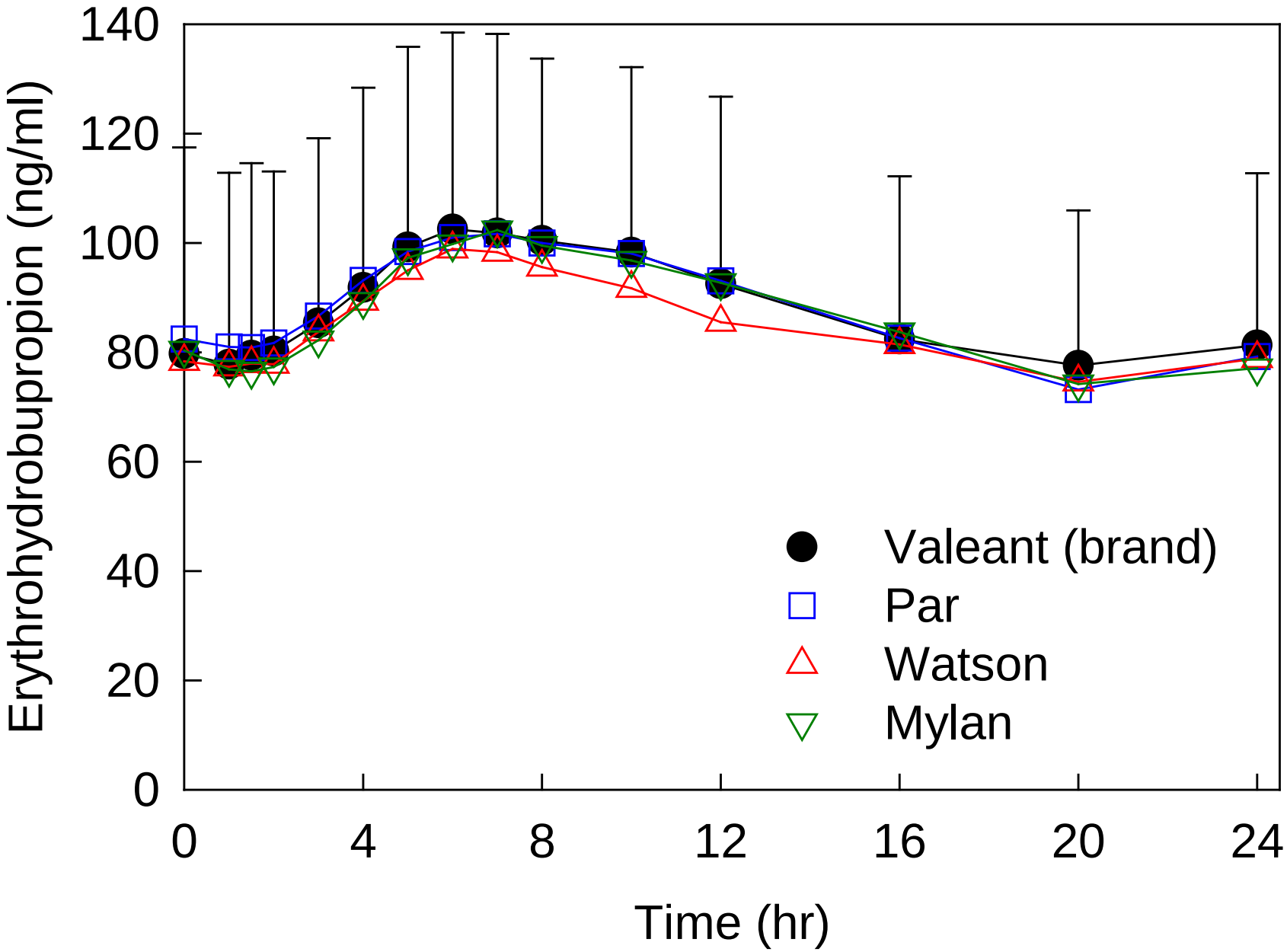
Bupropion plasma disposition



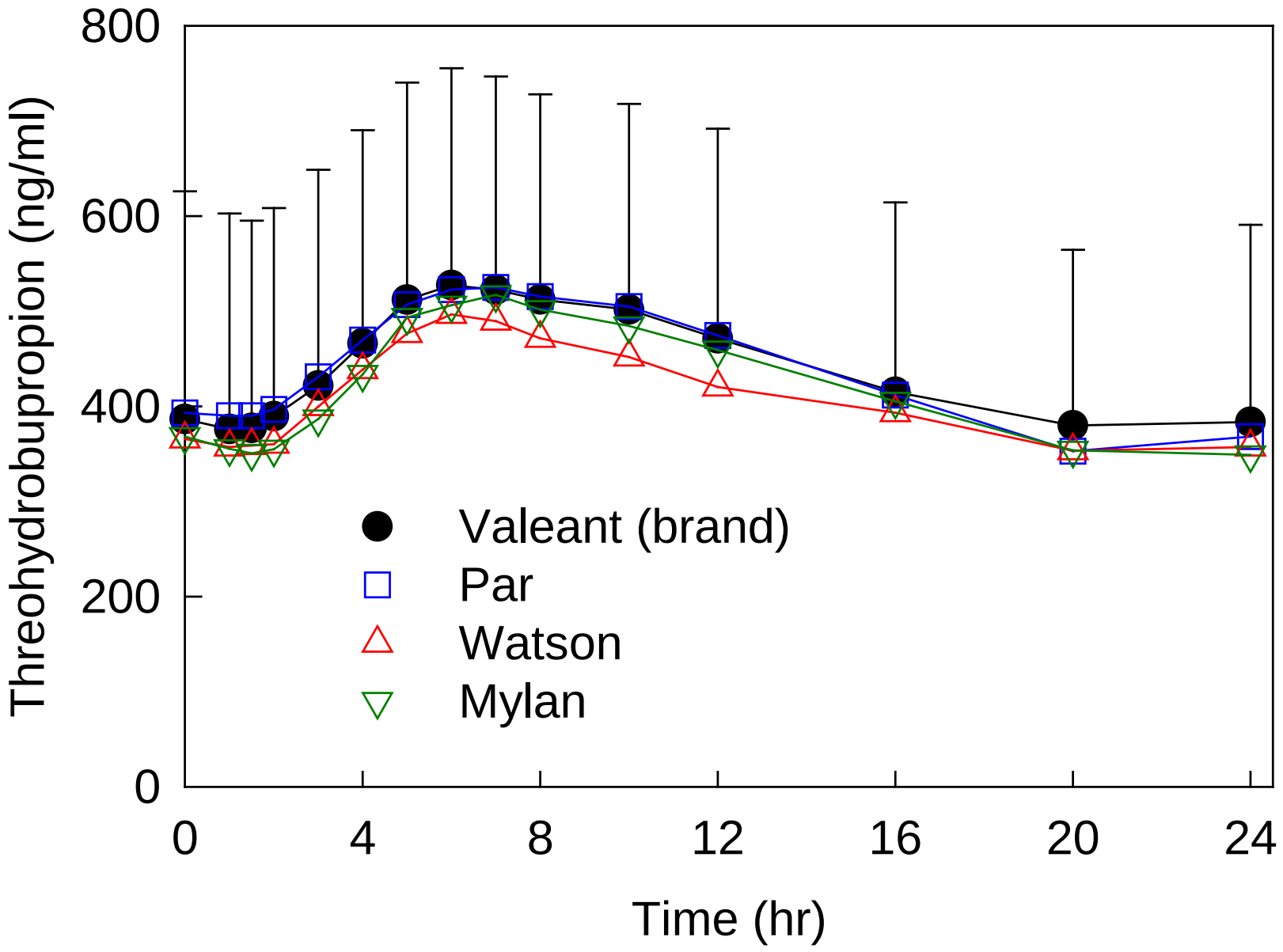
Bupropion plasma disposition



Bupropion plasma disposition



Bupropion plasma disposition

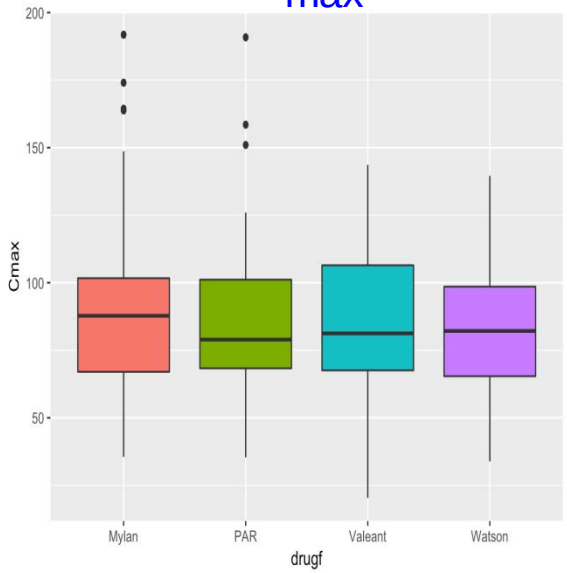


Bupropion plasma disposition

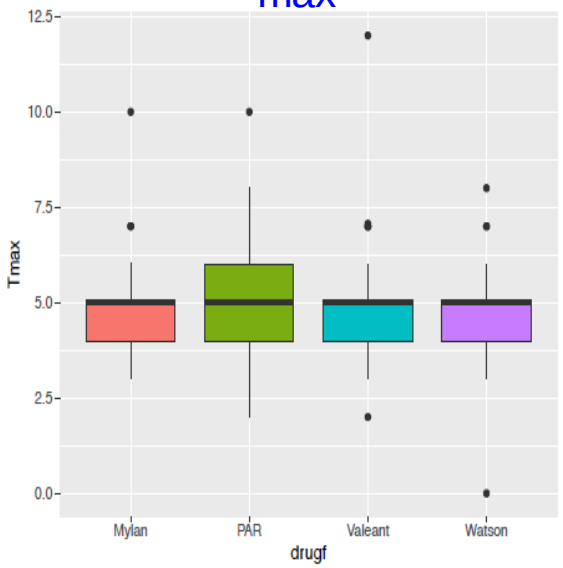
rac-bupropion

pharmacokinetic statistical comparison generic vs Brand

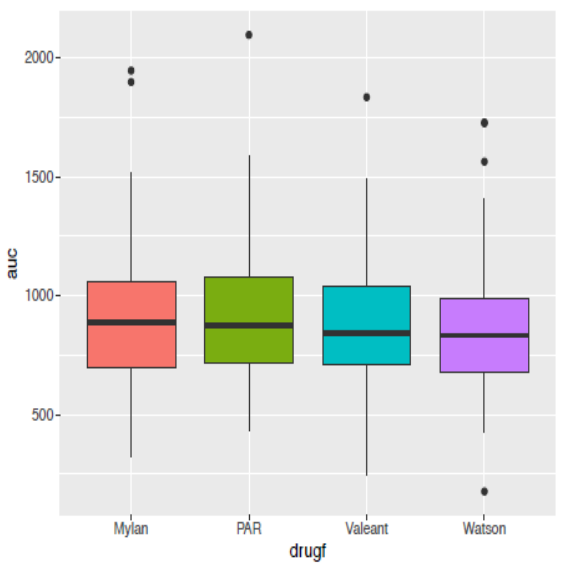
C_{max}



T_{max}



AUC



Parameter	Valeant (brand)	PAR	Watson	Mylan
C_{max} (ng/ml)[1]	81 (68-106)	79 (68-101)	82 (65-99)	88 (67-102)
bioequivalence (%)[2]		99 (94, 104)	97 (92, 102)	105 (99, 111)
T_{max} (hr)	4.9 ± 1.4	5.0 ± 1.6	4.8 ± 1.2	4.9 ± 1.1
bioequivalence		102 (95-109)	99 (91-106)	100 (93-108)
AUC (hr*ng/ml)	843 (708-1039)	875 (716-1077)	831 (681-989)	887 (700-1056)
bioequivalence (%)		103 (98, 108)	96 (92, 101)	102 (98, 107)

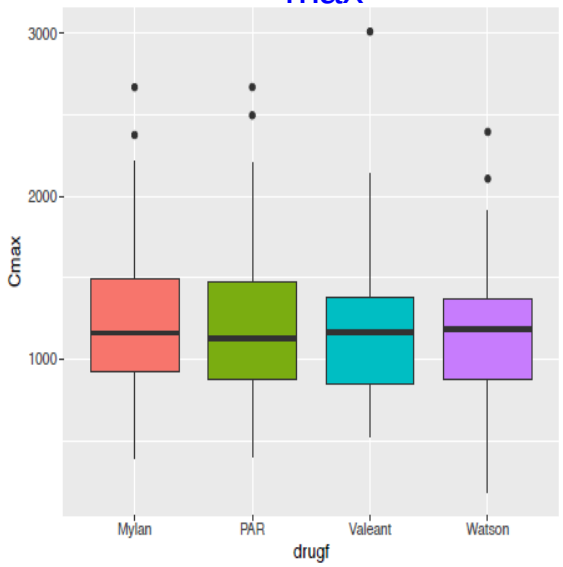
[1] C_{max} and AUC are median (Interquartile Range). T_{max} is mean (standard deviation)
[2] Bioequivalence is considered when 90% confidence interval is within 80%-125%

Bupropion plasma disposition

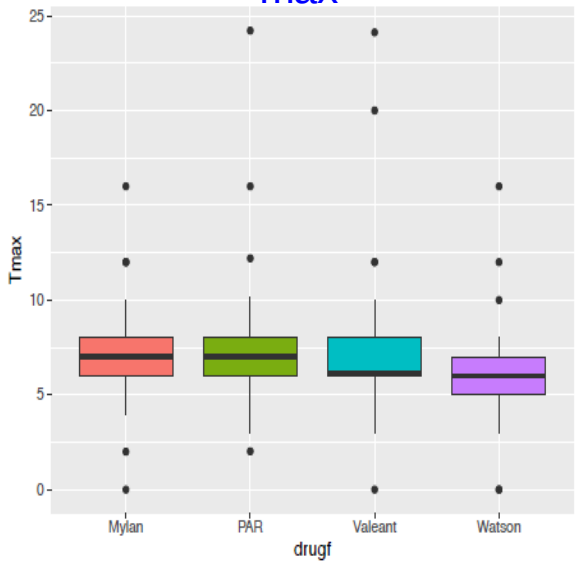
rac-hydroxybupropion

pharmacokinetic statistical comparison generic vs Brand

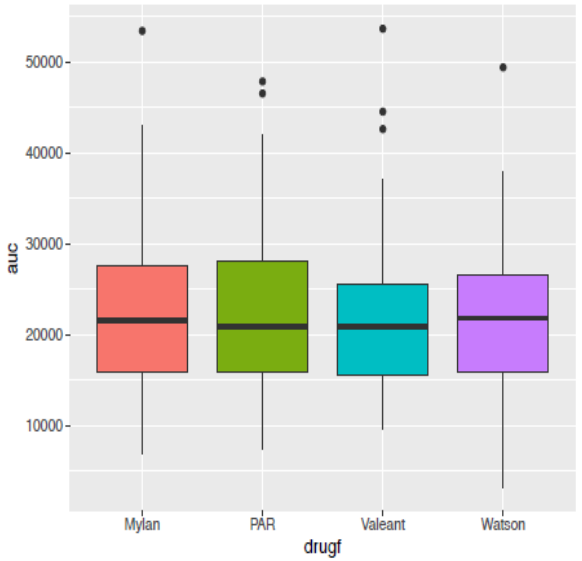
C_{max}



T_{max}



AUC



Parameter	Valeant (brand)	PAR	Watson	Mylan
C_{max} (ng/ml)[1]	1167 (849-1382)	1129 (877-1472)	1184 (881-1370)	1160 (923- 1495)
bioequivalence (%)[2]		101 (96, 106)	97 (92, 102)	102 (97, 108)
T_{max} (hr)	7.3 (3.3)	7.4 (3.0)	6.2 (2.1)	6.9 (2.4)
bioequivalence (%)		100 (90, 110)	88 (82, 95)	98 (90, 106)
AUC (hr*ng/ml)	20,860 (15,520-25,464)	20,853 (15,947-28,062)	21,846 (15,888-26,511)	21,566 (15,922-27,665)
bioequivalence (%)		102 (97, 108)	98 (93, 103)	103 (98, 109)

[1] C_{max} and AUC are median (Interquartile Range). T_{max} is mean (standard deviation)

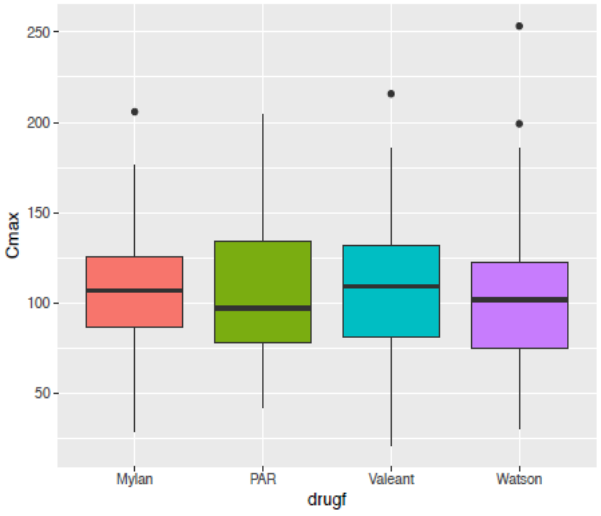
[2] Bioequivalence is considered when 90% confidence interval is within 80%-125%

Bupropion plasma disposition

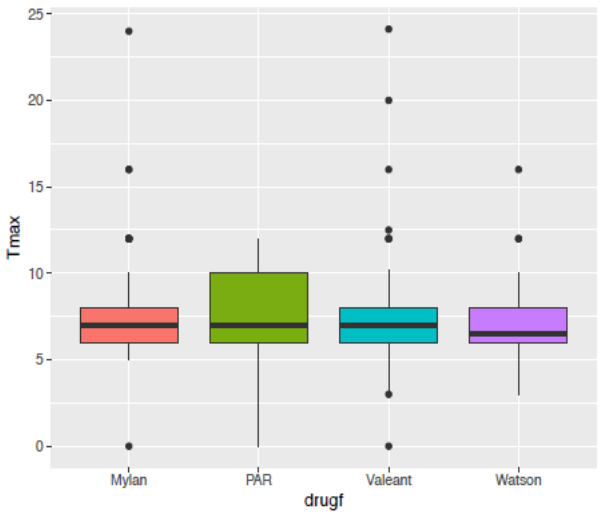
rac-erythrohydrobupropion

pharmacokinetic statistical comparison generic vs Brand

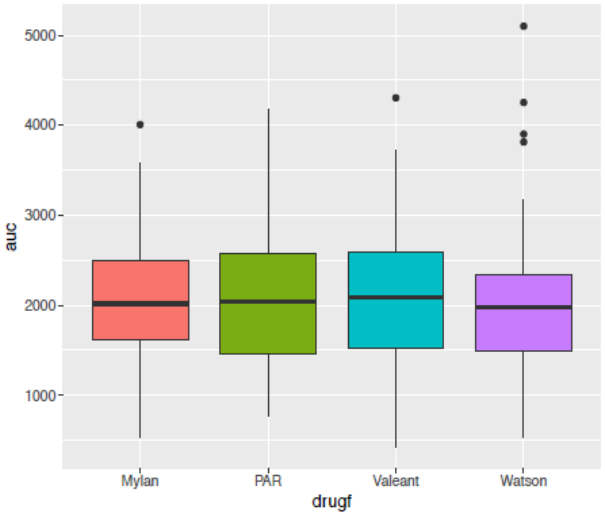
C_{max}



T_{max}



AUC



Parameter	Valeant (brand)	PAR	Watson	Mylan
C_{max} (ng/ml)[1]	109 (81-132)	97 (78-134)	102 (75-123)	107 (87-126)
bioequivalence (%)[2]		98 (93, 103)	94 (89, 100)	97 (91, 103)
T_{max} (hr)	7.5 (3.6)	7.6 (2.2)	6.9 (2.0)	7.9 (3.3)
bioequivalence (%)		105 (97, 114)	94 (86, 103)	107 (97, 117)
AUC (hr*ng/ml)	2089 (1521-2588)	2045 (1466-2571)	1981 (1488-2341)	2019 (1612-2496)
bioequivalence (%)		100 (94, 105)	96 (90, 102)	98 (92, 104)

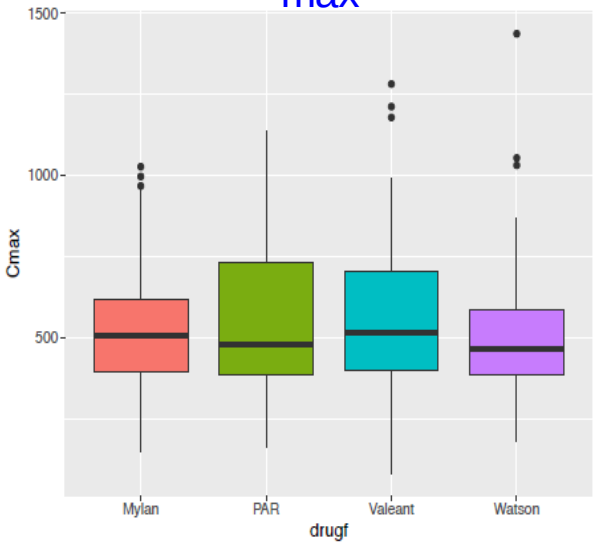
[1] C_{max} and AUC are median (Interquartile Range). T_{max} is mean (standard deviation)
[2] Bioequivalence is considered when 90% confidence interval is within 80%-125%

Bupropion plasma disposition

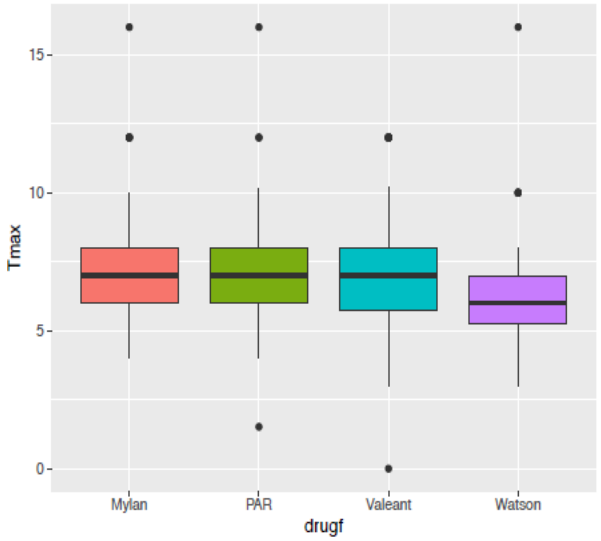
rac-threohydrobupropion

pharmacokinetic statistical comparison generic vs Brand

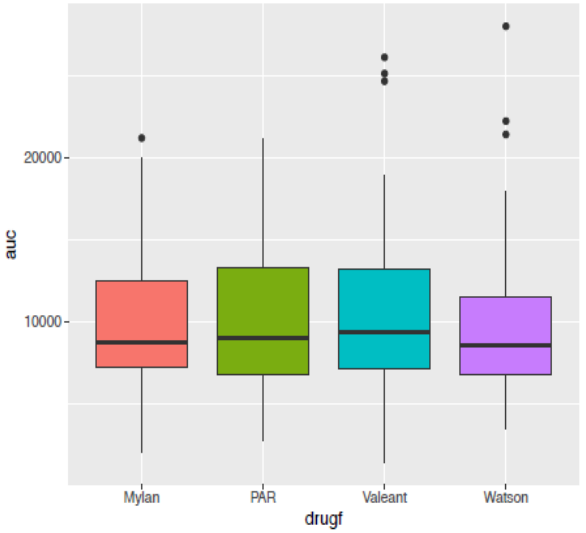
C_{max}



T_{max}



AUC



Parameter	Valeant (brand)	PAR	Watson	Mylan
C_{max} (ng/ml)[1]	516 (398-704)	479 (385-733)	466 (384-584)	506 (394-620)
bioequivalence (%)[2]		100 (95, 106)	94 (88, 100)	97 (91, 103)
T_{max} (hr)	7.0 (2.4)	7.5 (2.3)	6.3 (1.9)	7.2 (2.1)
bioequivalence (%)		107 (99, 115)	84 (82, 96)	102 (94, 110)
AUC (hr*ng/ml)	9384 (7210-13,268)	9049 (6849-13,346)	8573 (6829-11,567)	8780 (7252-12,490)
bioequivalence (%)		100 (94, 106)	94 (88, 101)	96 (90, 103)

[1] C_{max} and AUC are median (Interquartile Range). T_{max} is mean (standard deviation)
[2] Bioequivalence is considered when 90% confidence interval is within 80%-125%

Bupropion plasma disposition

rac-bupropion

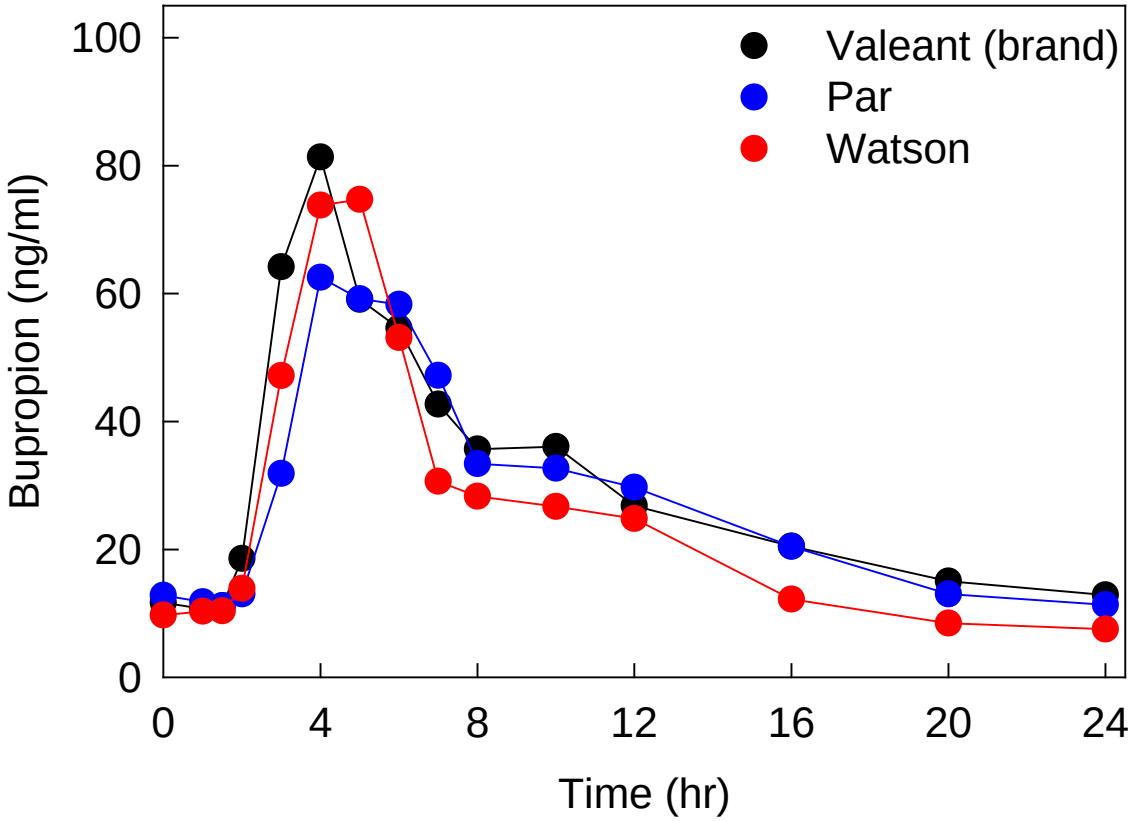
pharmacokinetic statistical comparison all products

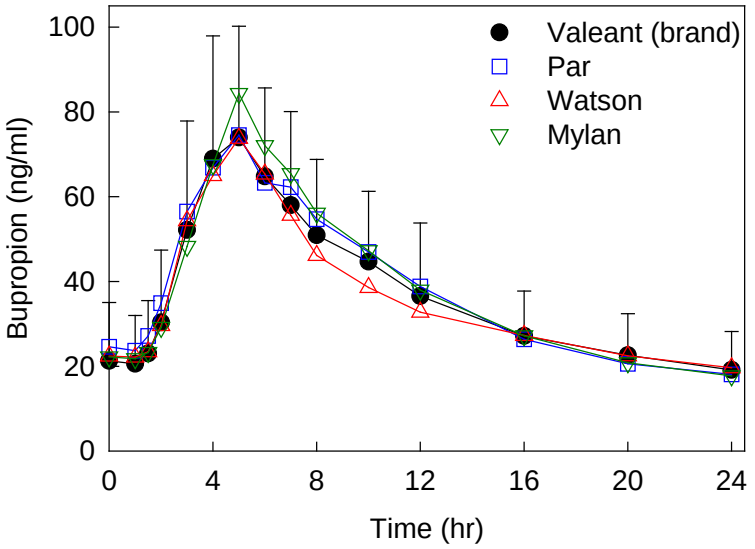
Parameter	Comparison	Mean	SE	P
AUC	Valeant (brand)-Mylan	-0.010	0.012	0.42
	Valeant (brand)-PAR	-0.013	0.012	0.29
	Valeant (brand)-Watson	0.017	0.012	0.17
	PAR-Mylan	0.003	0.012	0.80
	Watson-Mylan	-0.026	0.012	0.03
	Watson-PAR	-0.029	0.012	0.01
Cmax	Valeant (brand)-Mylan	-0.021	0.014	0.14
	Valeant (brand)-PAR	0.005	0.014	0.71
	Valeant (brand)-Watson	0.014	0.014	0.31
	PAR-Mylan	-0.026	0.014	0.06
	Watson-Mylan	-0.035	0.014	0.01
	Watson-PAR	-0.009	0.014	0.52

Unadjusted for multiple comparisons; nonsignificant when adjusted

Bupropion Disposition -- Subject 3

MDD Recurrence: PAR → Valeant (brand) → Watson, subject withdrawn following PK#3

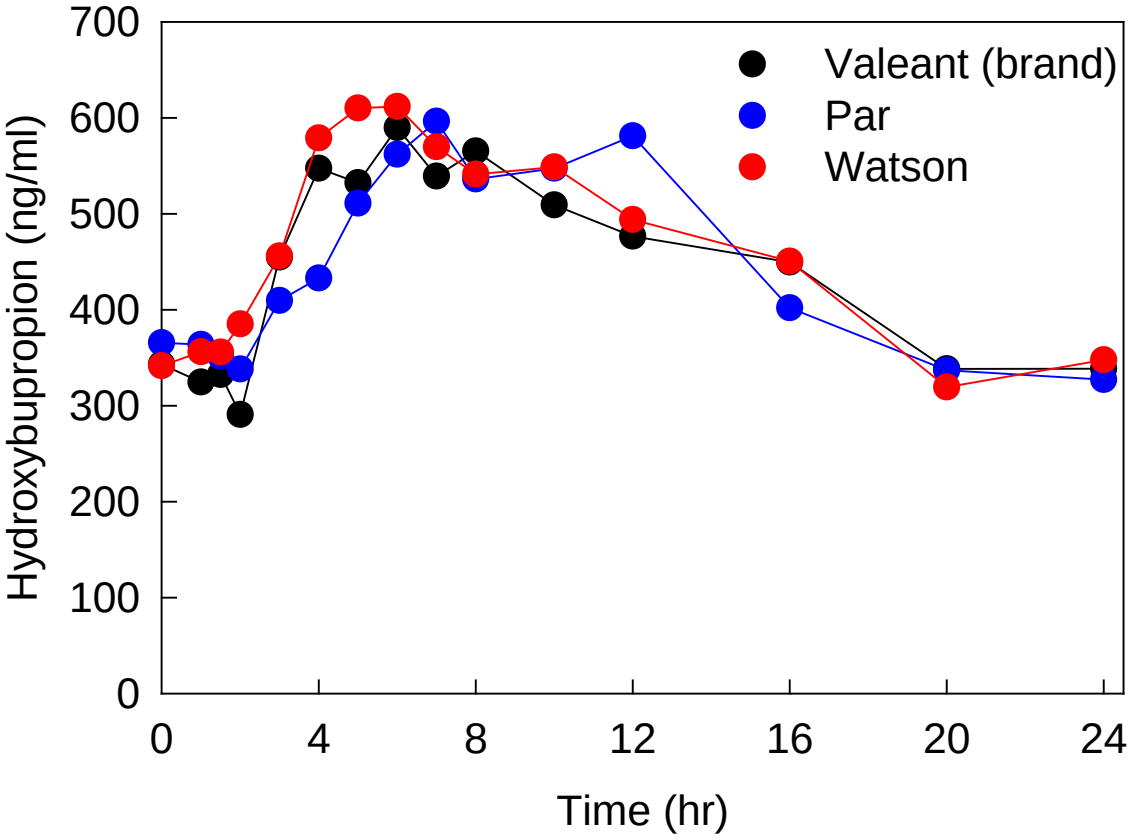




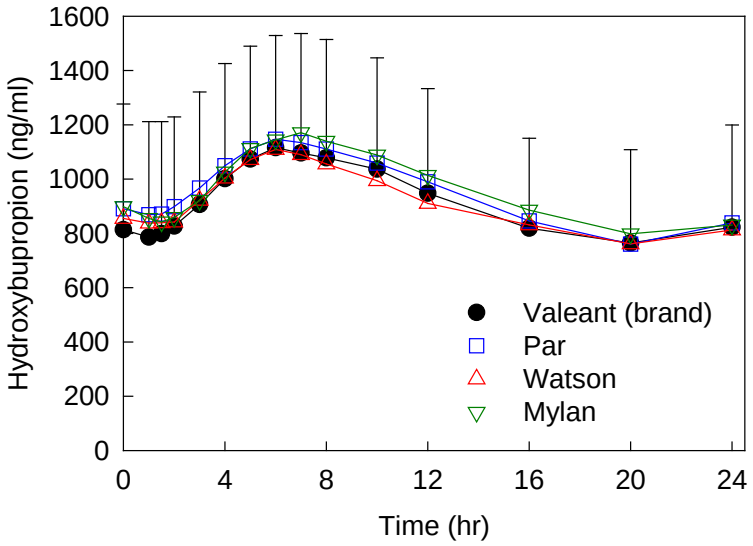
- Trough bupropion (ng/ml) ~50% that of population, C_{max} similar
- No difference between brand vs generics
- PK does not explain MDD recurrence on Watson

Bupropion Disposition -- Subject 3

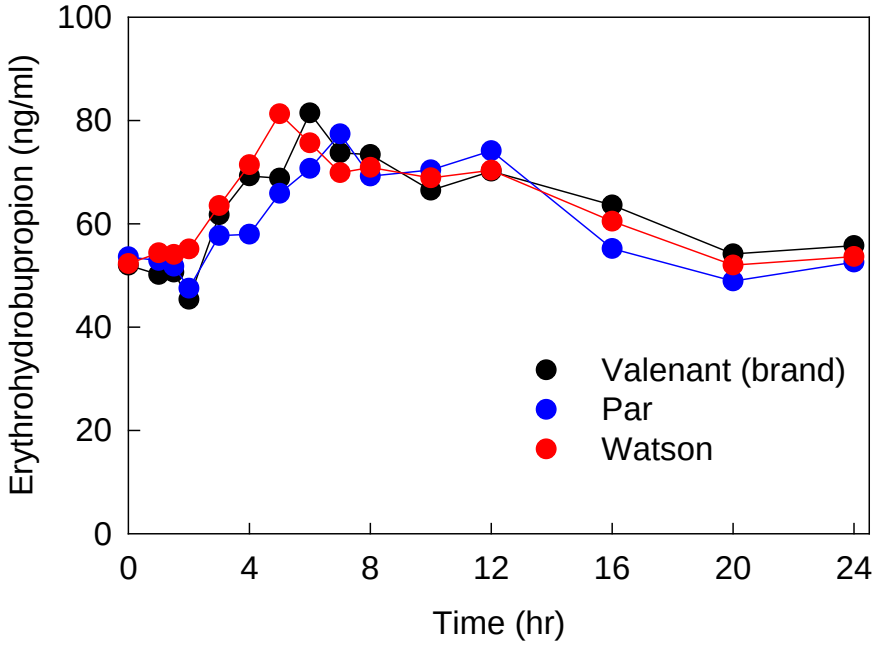
MDD Recurrence: PAR → Valeant (brand) → Watson, subject withdrawn following PK#3

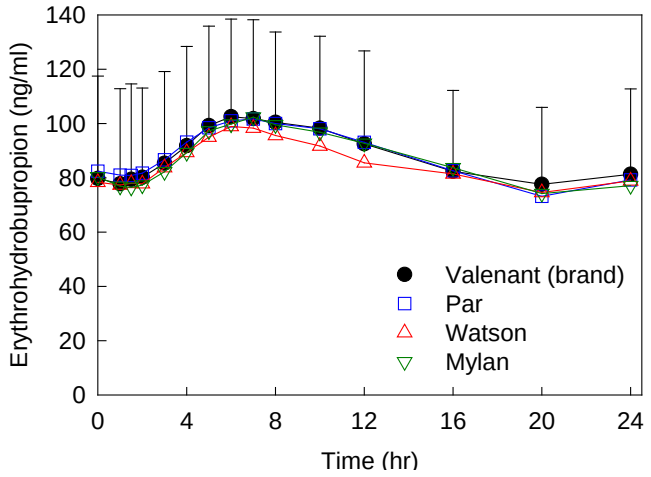


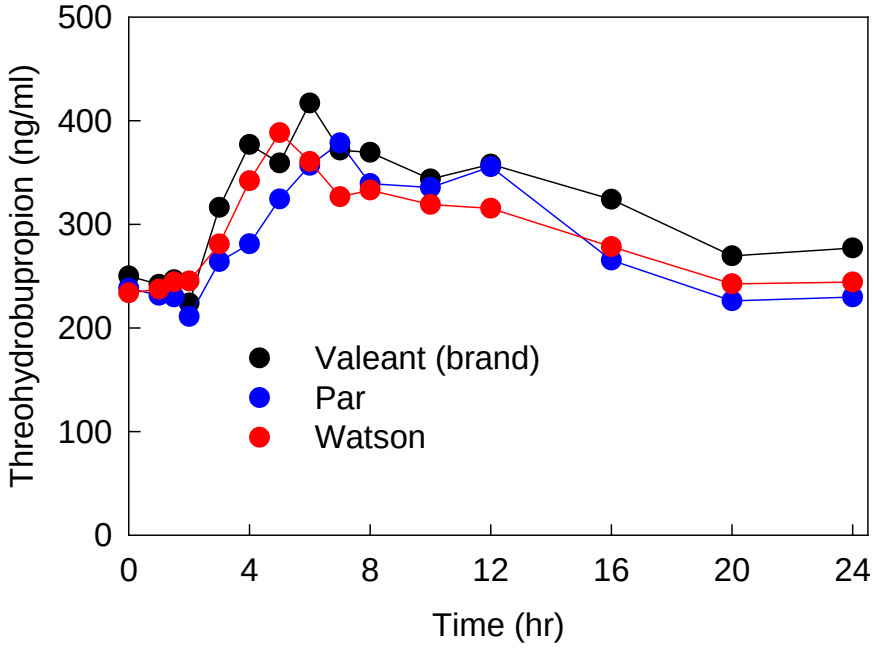
- Hydroxybupropion (ng/ml) trough & C_{max} ~50% that of population
- No difference between brand vs generics
- PK and PGX (*CYP2B6*1/*1*) does not explain MDD recurrence on Watson

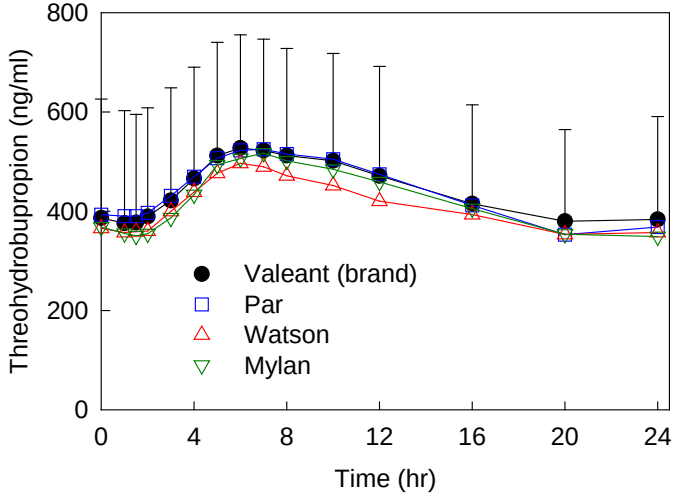


Bupropion Disposition -- Subject 3









- Erythro-/threo-hydrobupropion (ng/ml) ~75% that of population
- No difference between brand vs generics
- PK does not explain MDD recurrence on Watson

Bupropion bioequivalence - Conclusions

Aim 1: Bioequivalence using standard PK parameters (AUC, C_{max}) and definition (90% CI of generic/brand geometric mean within 80-125%) for bupropion (primary) and metabolites (secondary)

- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are bioequivalent to Valeant (brand) bupropion 300mg XL, based on *rac*-bupropion AUC, C_{max}, T_{max}
- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are not different, based on *rac*-bupropion AUC, C_{max}, T_{max}
- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are bioequivalent to Valeant (brand) bupropion 300mg XL, based on *rac*-hydroxybupropion, *rac*-erythrohydrobupropion and *rac*-threohydrobupropion AUC, C_{max}, T_{max}
- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are not different, based on *rac*-hydroxybupropion, *rac*-erythrohydrobupropion and *rac*-threohydrobupropion AUC, C_{max}, T_{max}

Inter-individual differences in bupropion disposition are greater than intra-individual (inter-product) differences

Bupropion clinical effects

Aim 2:

Compare patients' clinical response to each bupropion 300mg XL product, using objective, well-validated measures of depression response and side effects

1. **Clinic-based measurement of antidepressant effectiveness and side effects**
2. **Cellphone-based Ecological Daily Assessment (EDA) evaluation of antidepressant effectiveness and side effects**

Primary outcome:

Relapse of depression, defined using MADRS and SCID depression module

- ≥2 point increase from average baseline open-label lead-in phase MADRS score, on 2 consecutive evaluations, triggers SCID depression assessment.
- If the SCID reveals current MDD, subject is considered to have relapsed

Secondary outcome:

Symptomatic change in depression (MADRS score) & side effects (Antidepressant Side Effect Checklist scores) determined at the every 3-week interviews

Study design rationale

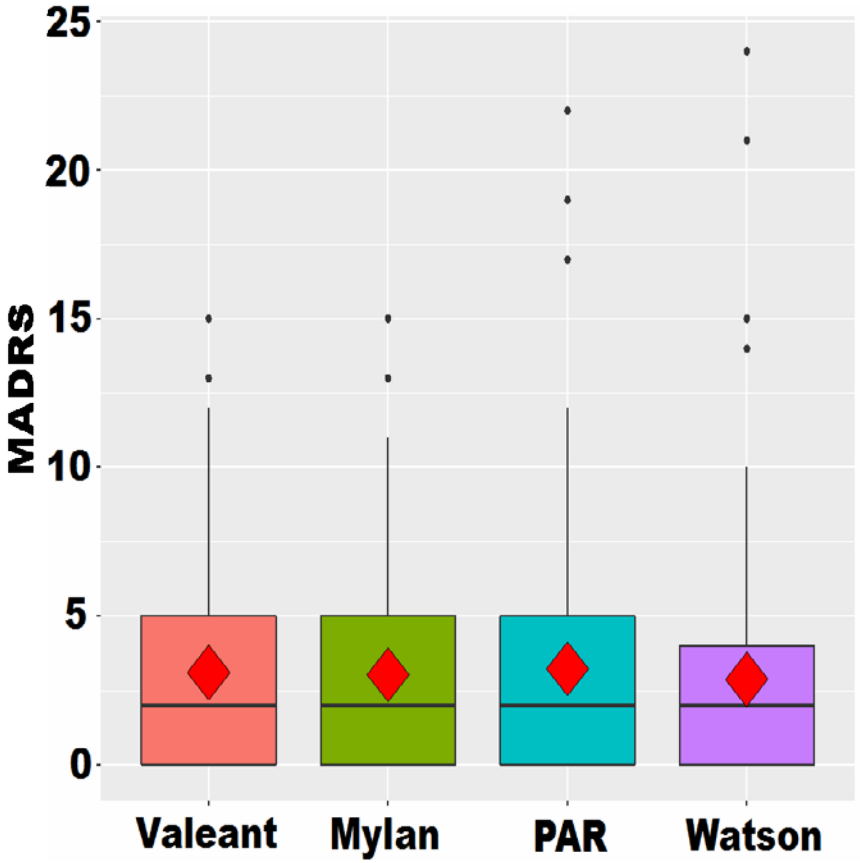
- Randomized withdrawal design studies ("maintenance trials") are the most robust antidepressant trials.*
- In this design, patients who are known responders to an antidepressant are randomized to maintain it or be tapered to a placebo
- In such studies, the relapse rate on placebo is substantial: 40% (vs. 20% who maintain the drug)
- If patients who are responding to bupropion XL are switched to an inferior version, this should be reflected in worsening of depression

*Borges: J Clin Psychiatry 2014;75:205-214

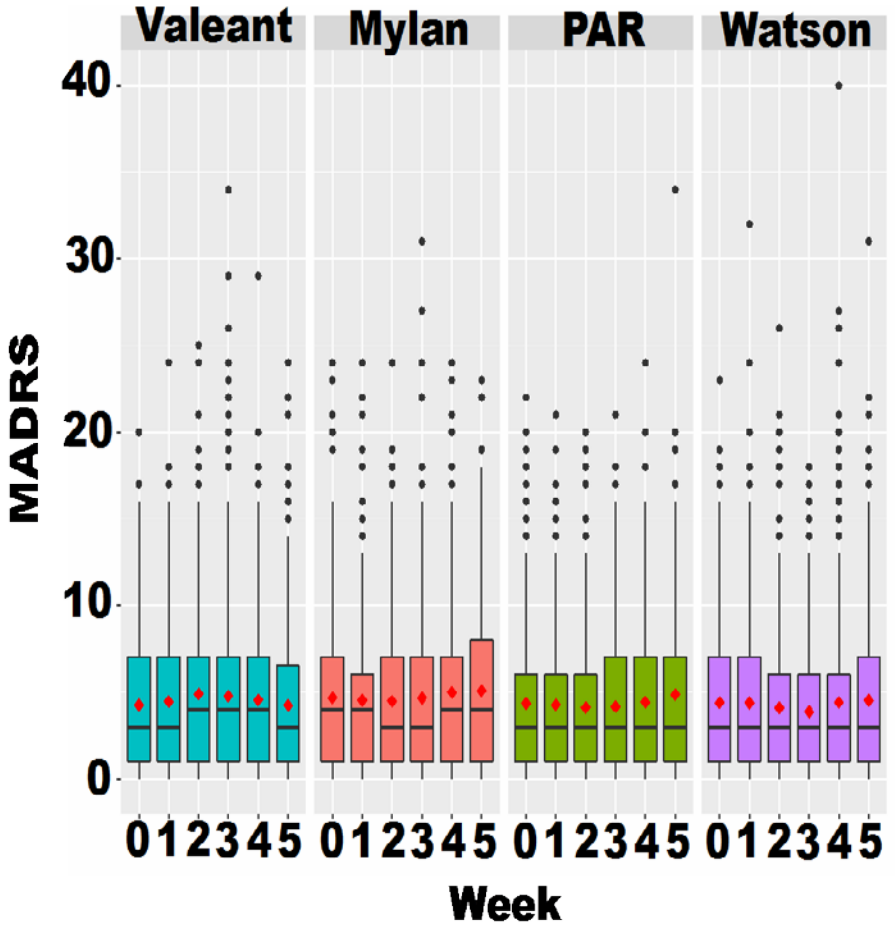
Bupropion clinical effects on depression

Depressive symptoms assessed via Montgomery Asberg Depression Rating Scale (MADRS)

MADRS from Clinic Visit

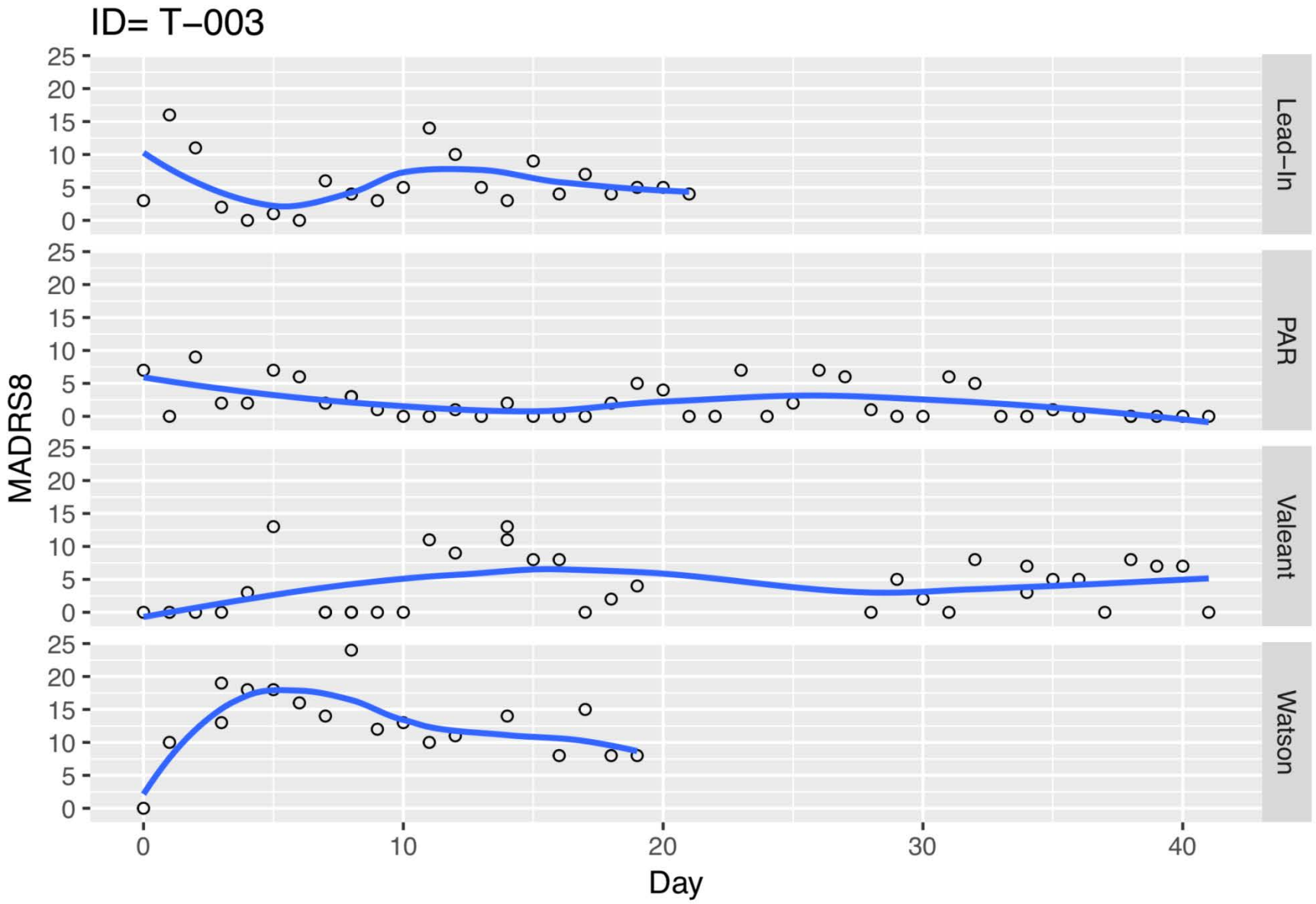


MADRS from Cell Phone



Only 2 participants had a relapse of major depression:
one in lead-in and one during randomized phase

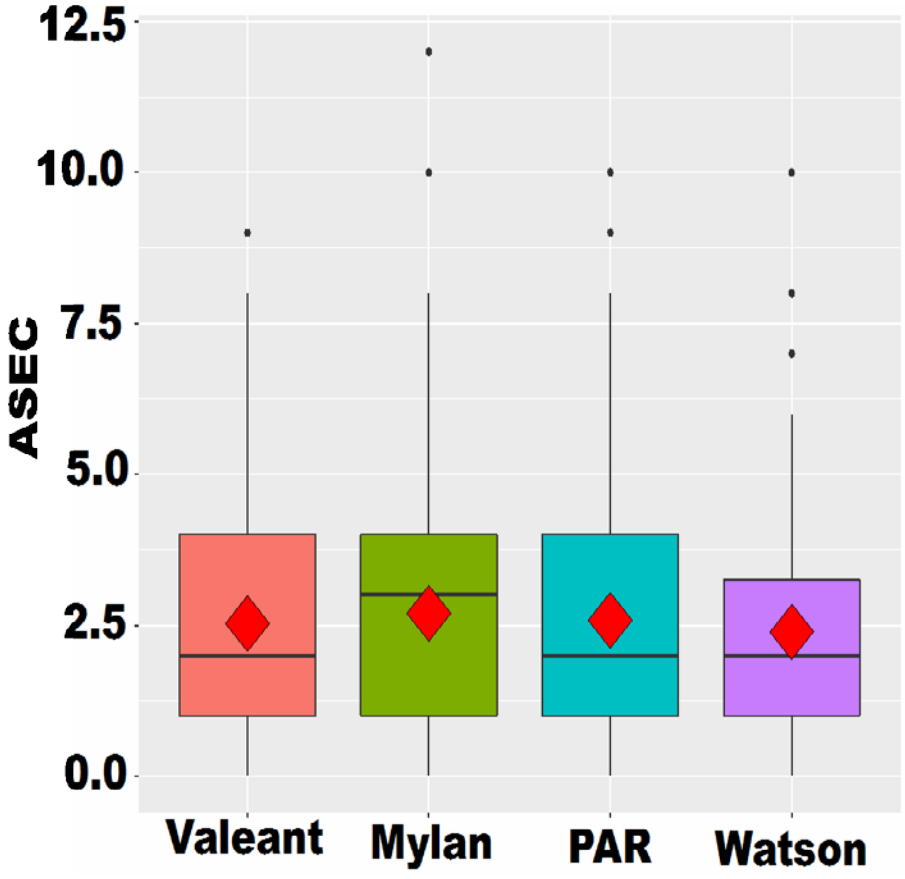
Bupropion clinical effect -- Subject 3



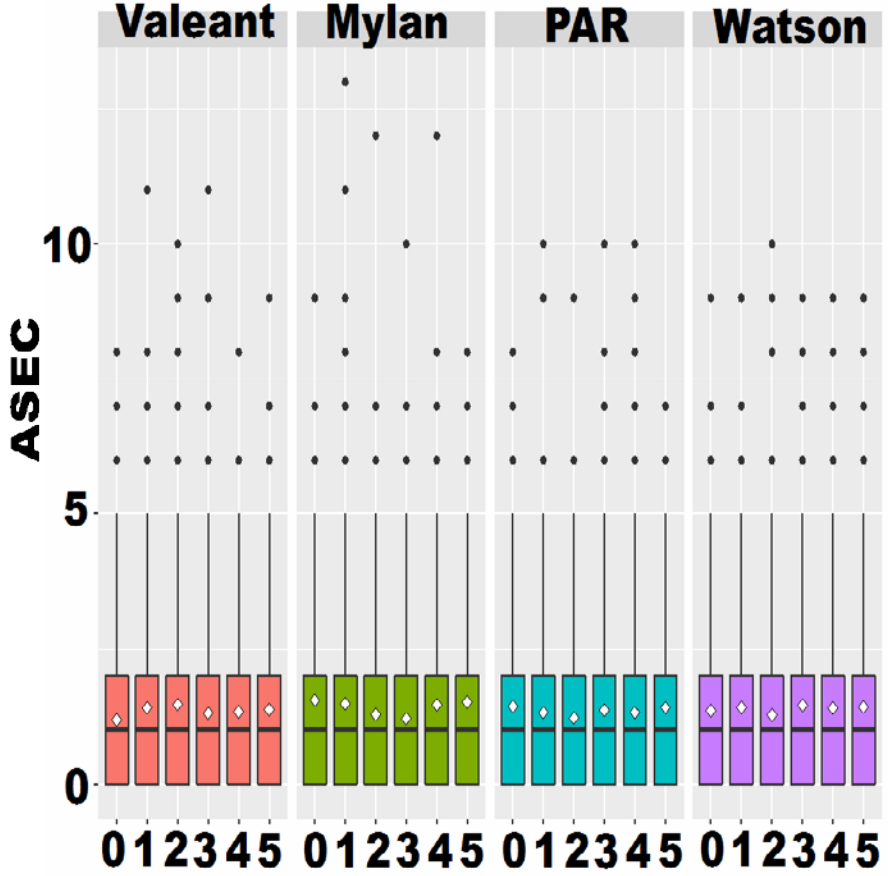
Bupropion clinical effects: side effects

assessed via Antidepressant Side Effects Checklist (ASEC)

ASEC from Clinic Visit



ASEC from Cell Phone



Bupropion therapeutic equivalence - Conclusions

Aim 2:

Compare patients' clinical response to each bupropion 300mg XL product, using objective, well-validated measures of depression response and side effects

- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are therapeutically equivalent (antidepressant effectiveness) to Valeant (brand) bupropion 300mg XL and to each other
  - Macro: Only one relapse in the randomized trial
  - Micro: No evidence of symptomatic worsening over time (higher MADRS scores)

- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are therapeutically equivalent (side effects) to Valeant (brand) bupropion 300mg XL and to each other
  - No evidence of increased side effects when switching from one product to another

Bupropion clinical effects

Aim 3:

Compare patient perceptions of clinical differences (release patterns, antidepressant effectiveness, adverse events) between all bupropion 300mg XL products (brand vs generics, and between generics), using innovative methods for assessing patient perspectives

Primary outcome:

Completion questionnaire:

Among the 4 bottles of study drug did you notice any difference:

- between them?
- in how they made you feel?
- in how they made you feel at different times of the day?
- in how they affected your depression?
- in any drug side effects?

Bupropion clinical effects

Aim 3: Compare patient perceptions of clinical differences

Among the 4 bottles of study drug did you notice any difference:	No	Yes	P-value
between them?			0.17
Valeant (brand)	9	3	
Mylan	13	2	
PAR	4	5	
Watson	15	6	
in how they made you feel?			0.34
Valeant (brand)	4	3	
Mylan	10	3	
PAR	5	6	
Watson	9	3	
in how they made you feel at different times of the day?			0.49
Valeant (brand)	4	0	
Mylan	3	1	
PAR	2	0	
Watson	3	0	
in how they affected your depression?			0.40
Valeant (brand)	6	4	
Mylan	8	3	
PAR	3	4	
Watson	8	2	
in any drug side effects?			1.00
Valeant (brand)	7	1	
Mylan	7	1	
PAR	5	1	
Watson	7	1	

Bupropion bioequivalence - Conclusions

Aim 3:

Compare patient perceptions of clinical differences (release patterns, antidepressant effectiveness, adverse events) between all bupropion 300mg XL products (brand vs generics, and between generics), using innovative methods for assessing patient perspectives

- Generic bupropion 300mg XL products (Mylan, PAR, Watson) are not different from Valeant (brand) bupropion 300mg XL and each other based on patient perceptions of clinical effects

Bioequivalence and clinical effects of generic and brand bupropion

Bupropion 300mg XL generic products (PAR, Watson, Mylan) were bioequivalent and clinically equivalent to Valeant (brand) product, and to each other