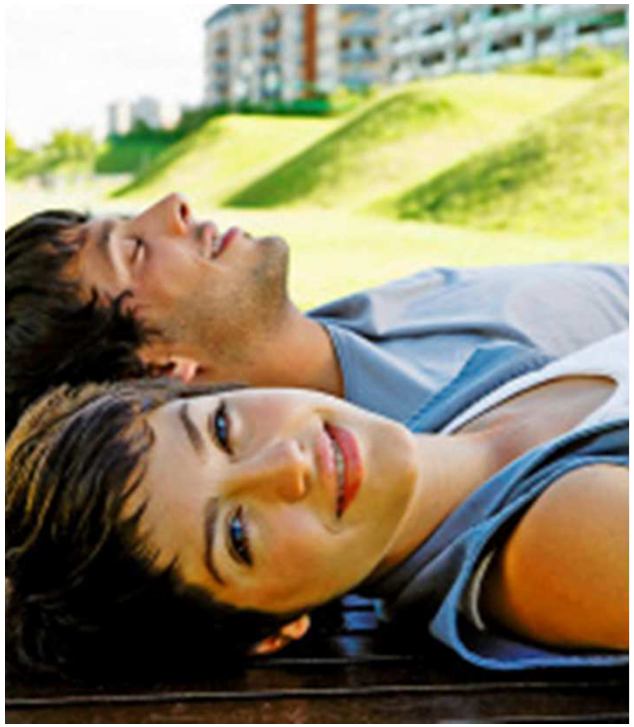
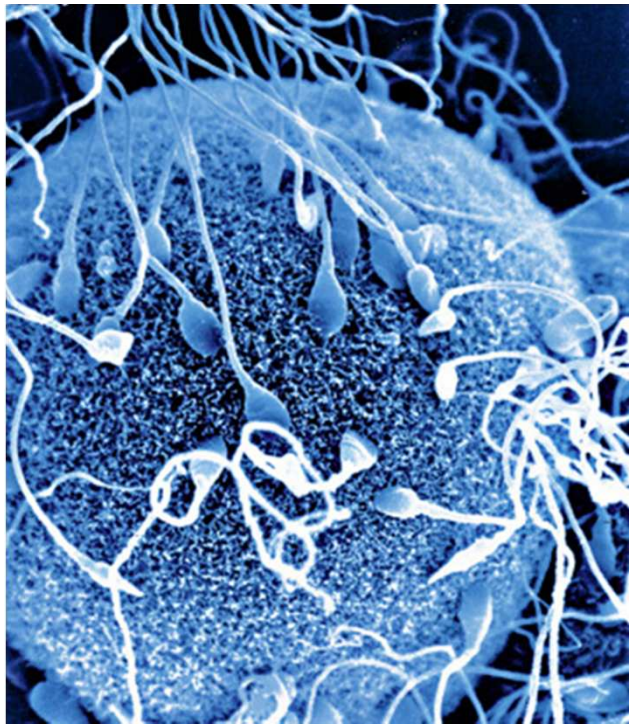
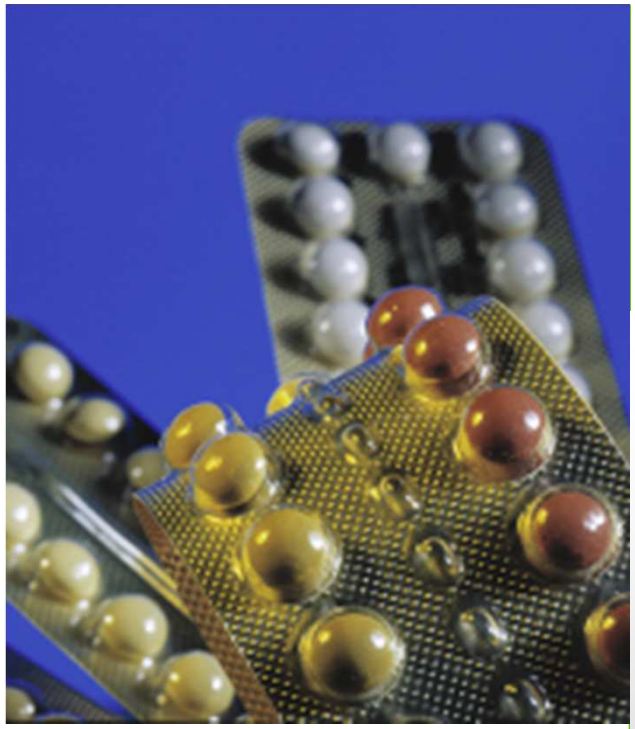




Science For A Better Life

Drug interactions with hormonal contraceptives (HCs)

Assessing potential drug interactions with HCs during drug development at Bayer

Nov 9th, 2015 - Joachim Höchel, Herbert Wiesinger

Disclosures

- Joachim Höchel and Herbert Wiesinger are full time employees of Bayer Pharma AG, Berlin, Germany
- Joachim Höchel and Herbert Wiesinger are stockholder in Bayer (BAY001)

Agenda

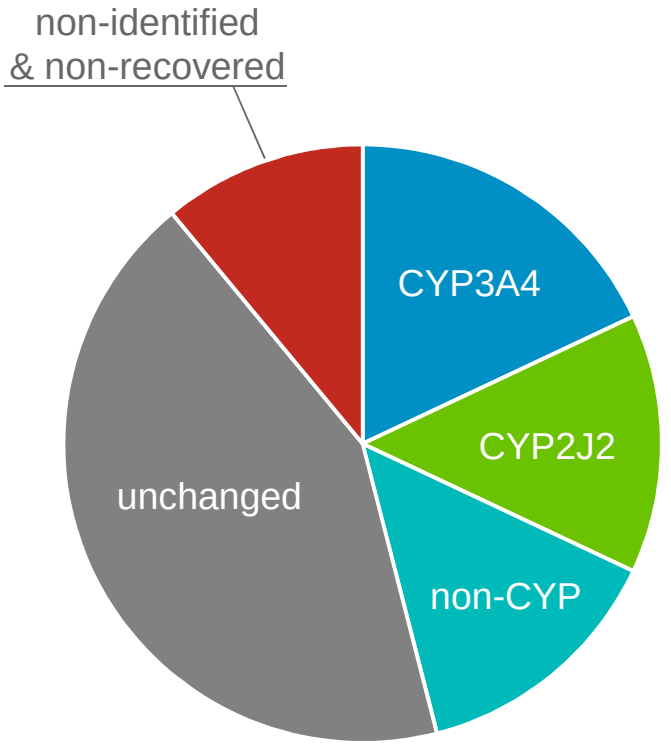
- Drug development paradigm at Bayer
- Effect of CYP3A4 inhibitors/inducers on HCs
  - Overview of DDI experience with HCs at Bayer
  - Case example oral HCs
  - Case example transdermal contraceptive patch
- Progestins and estrogens as perpetrator drugs
- Assessment of clinical relevance of findings

Drug development paradigm for assessing DDIs at Bayer

Investigational compound as victim drug (I)

Understanding clearance mechanisms and elimination pathways, e.g.

- ***In vitro*** (liver microsomes, human hepatocytes, recombinant isoenzymes, isoenzyme specific inhibitors, transfected cells) experiments:
  - Metabolite identification
  - CYP/UGT reaction phenotyping, other enzymes
  - Transporter substrate characteristics
- ***In vivo*** mass balance / biotransformation pathways in humans
- Absolute bioavailability study in humans



Rivaroxaban clearance
Mück et al. Br J Clin Pharmacol. 2013

Drug development paradigm for assessing DDIs at Bayer

Investigational compound as victim drug (II)

Assessment of *in vivo* DDI potential in humans, e.g.

- Evaluation of DDI potential with enzymes contributing ≥25% of total clearance pathway (confirming *in vitro* results)
- **Mechanistic approach** (supported by physiological based PK modeling), e.g. starting with most potent inhibitor of metabolic enzymes/transporter
- Complemented by
  - Broad *in vitro* screening of potential co-medications
  - *In vivo* DDI studies for common co-medications
  - Population PK DDI covariate analysis in patient studies

Drug development paradigm for assessing DDIs at Bayer

Investigational compound as perpetrator drug

Identification/exclusion of inhibitory/induction potential

- ***In vitro***
  - CYP/UGT inhibition (human liver microsomes, human hepatocytes, incl. CYP3A4 mechanism based inhibition) experiments using enzyme-selective substrates
  - CYP induction (human hepatocytes) experiments
  - Transporter inhibition
  - DDI studies (selected co-medications)

Assessment of *in vivo* DDI potential

- Mechanistic approach based on *in vitro* data using a sensitive substrate of affected metabolic enzymes or transporter
- DDI study applying therapeutic dose of perpetrator drug

Timing of drug metabolism/ transporter studies

***In vitro* studies:**

- Metabolite identification
- CYP & transporter
  - phenotyping
  - inhibition
- CYP induction

Refined DDI package in vitro & in vivo

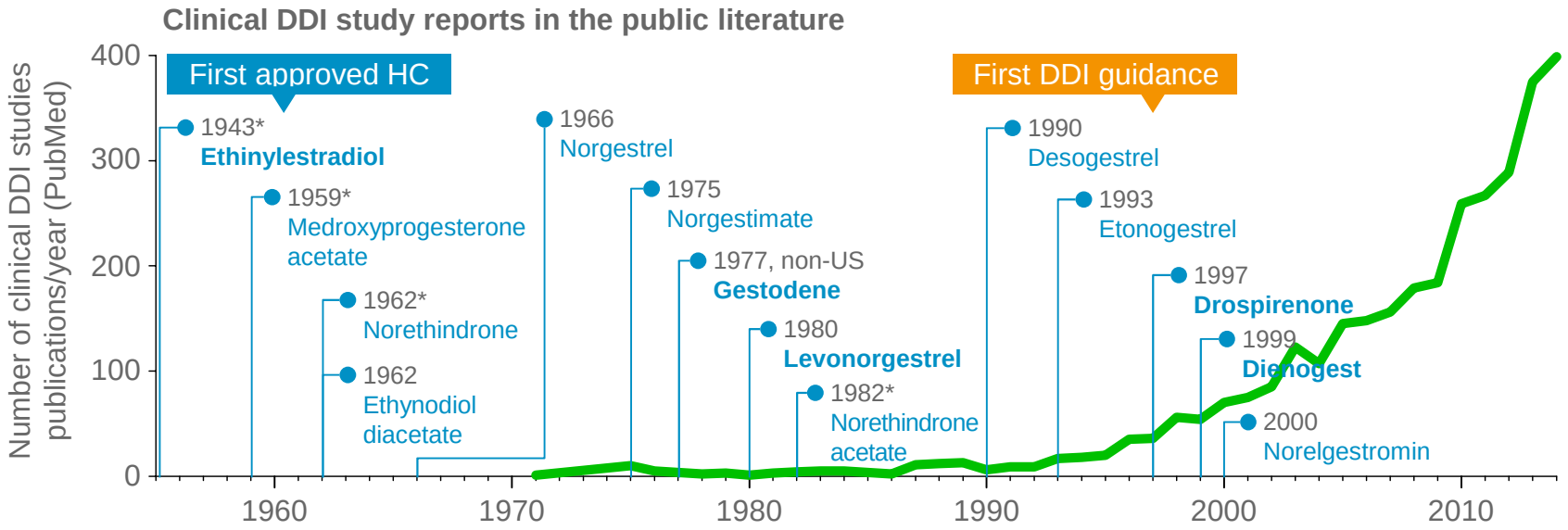
Potential *in vitro* studies:

- UGT phenotyping
- UGT inhibition
- Others: e.g. AKR, SULT

Embryo-fetal toxicity studies (before use in women of childbearing potential)

HC development in the context of emerging DDI experience

- Most HCs developed before established availability of tools to investigate CYP enzymes and transporters and general awareness of DDIs



Marketed HCs in US (status Oct 2015); USAN filing year (or first FDA approval year*)

Agenda

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  - Overview of DDI experience with HCs at Bayer
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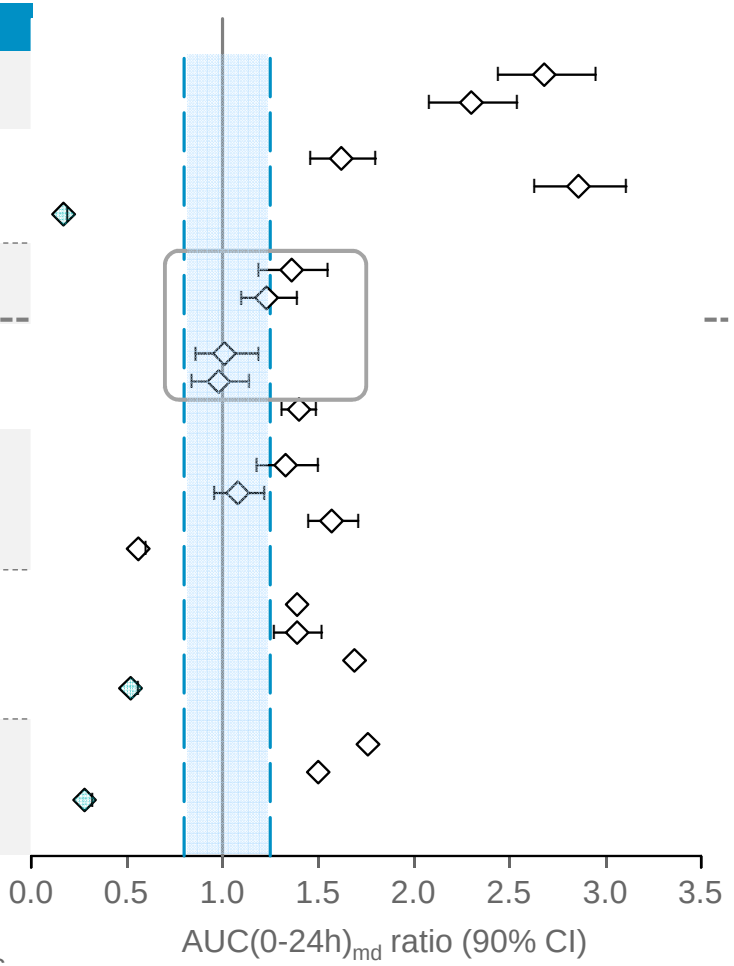
  - Case example transdermal contraceptive patch
- Progestins and estrogens as perpetrator drugs
- Assessment of clinical relevance of findings

Clinical DDI experience with HCs at BAYER - HCs as victim drug (CYP3A4 perpetrator drugs)

Victim drug	Perpetrator drug
Drospirenone	Ketoconazole Ketoconazole
Dienogest	Erythromycin Ketoconazole Rifampicin
Gestodene*	Erythromycin Ketoconazole
Ethinylestradiol (EE)	Erythromycin Ketoconazole Ketoconazole
Estradiol (E2)	Erythromycin Ketoconazole Ketoconazole Rifampicin
Estrone (E2 metabolite)	Erythromycin Ketoconazole Ketoconazole Rifampicin
Estrone sulfate (E2 metabolite)	Erythromycin Ketoconazole Rifampicin



* Marketed in >70 countries world-wide, not in US

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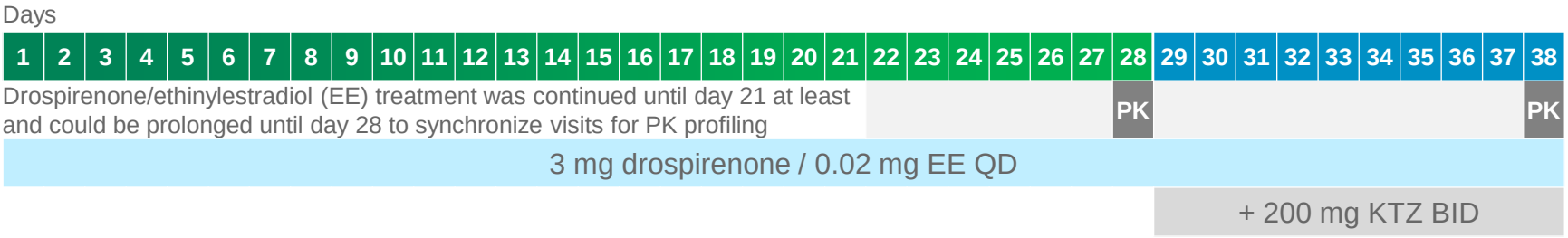
CYP3A4 inhibition (HC as victim drug)
Effect of ketoconazole (KTZ) on YAZ

Study design: open-label, one-way crossover in fertile women

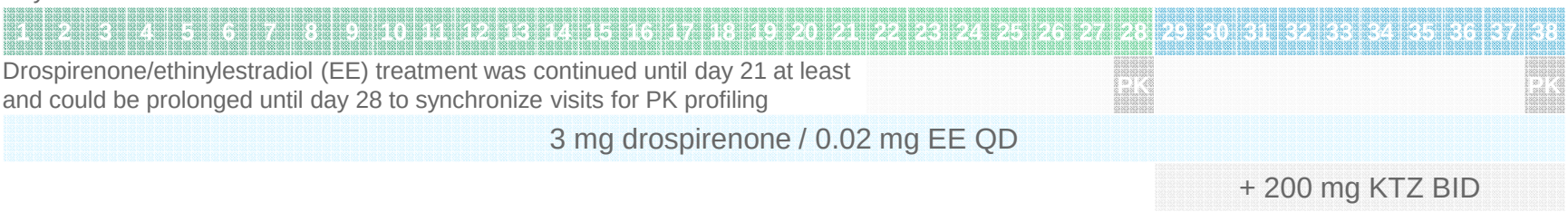
Cohort 1 (N=22 per arm)



Interim analysis

The group sequential approach allowed to stop the study for futility (or success, if applicable) after the planned interim analysis

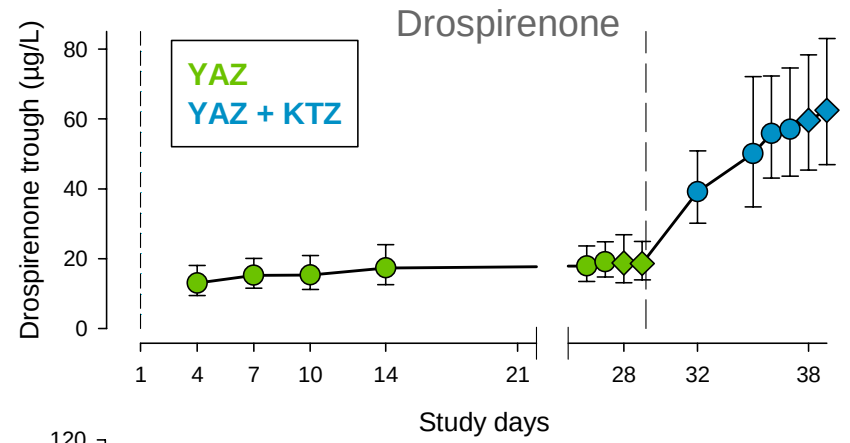
Cohort 2, optional (N=22 per arm)

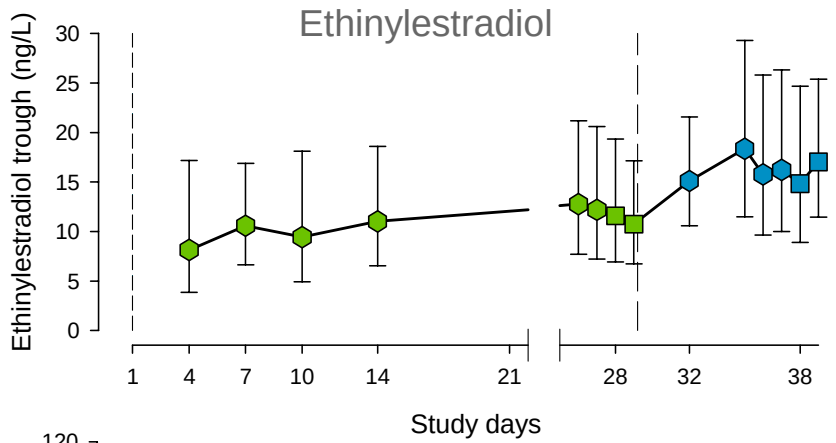


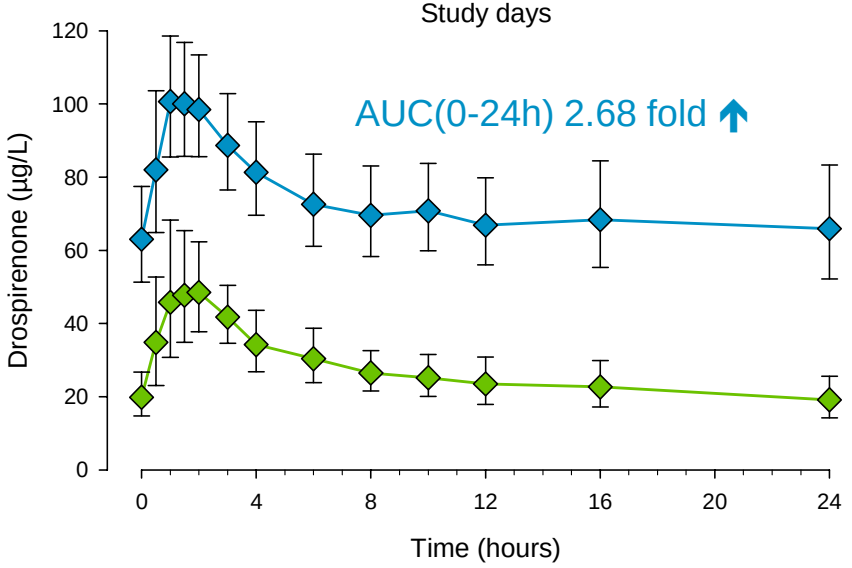
QD: once daily, BID: twice

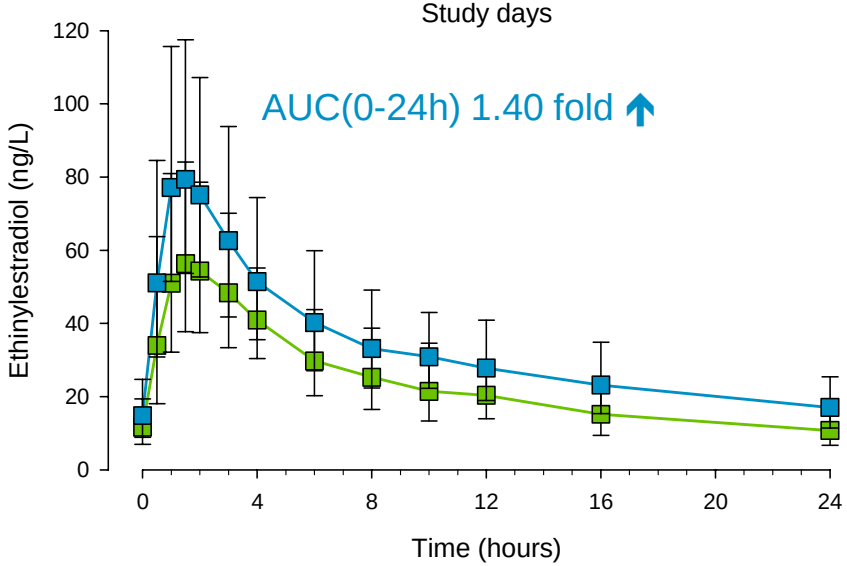
Wiesinger et al. Br J Clin Pharmacol. 2015

CYP3A4 inhibition (HC as victim drug)
Effect of KTZ on YAZ - Results









CYP3A4 inhibition (HC as victim drug) Effect of KTZ on YAZ - Conclusions

- CYP3A4 contributes to elimination of EE and drospirenone
- Observed exposure increases are not expected to translate into increased safety risks
- General HC “class label” applicable (complemented by specific study data)

Drospirenone family USPI’s (2015)
Section 7 DRUG INTERACTIONS
Substances increasing the plasma concentrations of COCs: …

Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice **can increase the plasma concentrations of the estrogen or the progestin or both.** …

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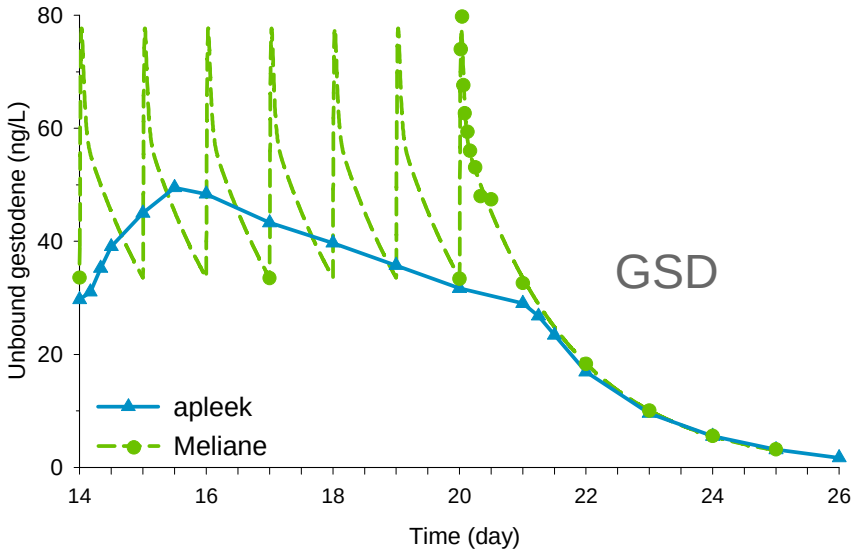
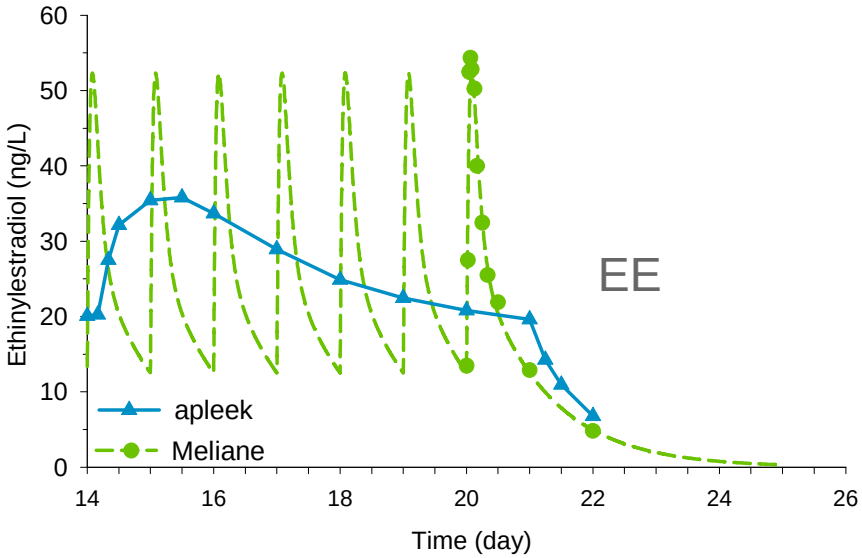
Non-oral administration
Transdermal contraceptive patch

apleek a once-a-week, 21 day regimen patch for HC*

- Exposures correspond to a combined oral contraceptive containing 0.02 mg EE and 0.06 mg gestodene (GSD)

Meliane once-daily oral tablet (0.02 mg EE / 0.075 mg GSD)





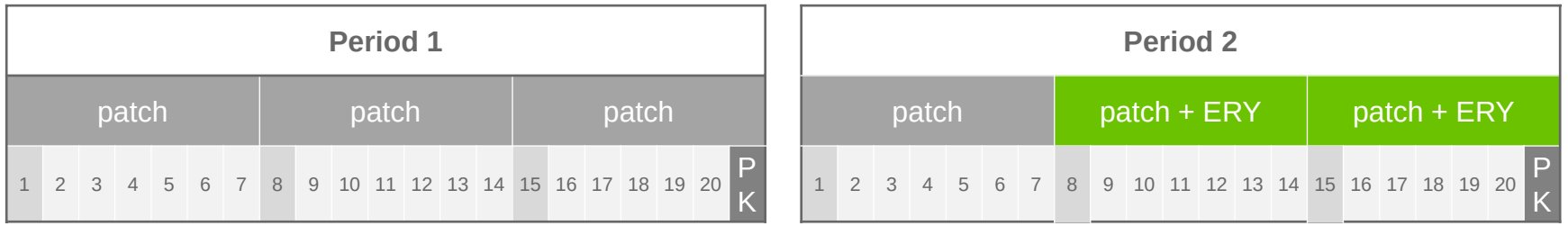
* apleek contains 0.55 mg ethinylestradiol (EE) and 2.1 mg gestodene (GSD), not approved in US

CYP3A4 inhibition (HC as victim drug)

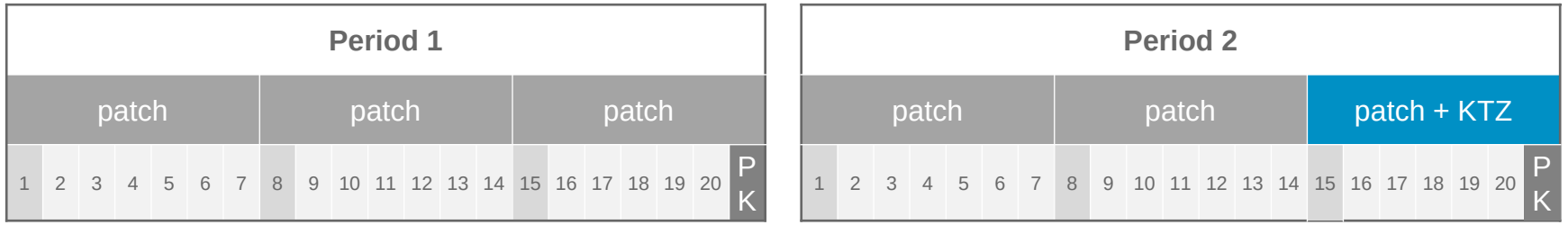
Effect of erythromycin (ERY) and KTZ on apleek

Study design: open-label, one-way crossover in fertile women

Erythromycin (ERY) Day 8-21: 500 mg TID



Ketoconazole (KTZ) Day 15-21: 200 mg BID

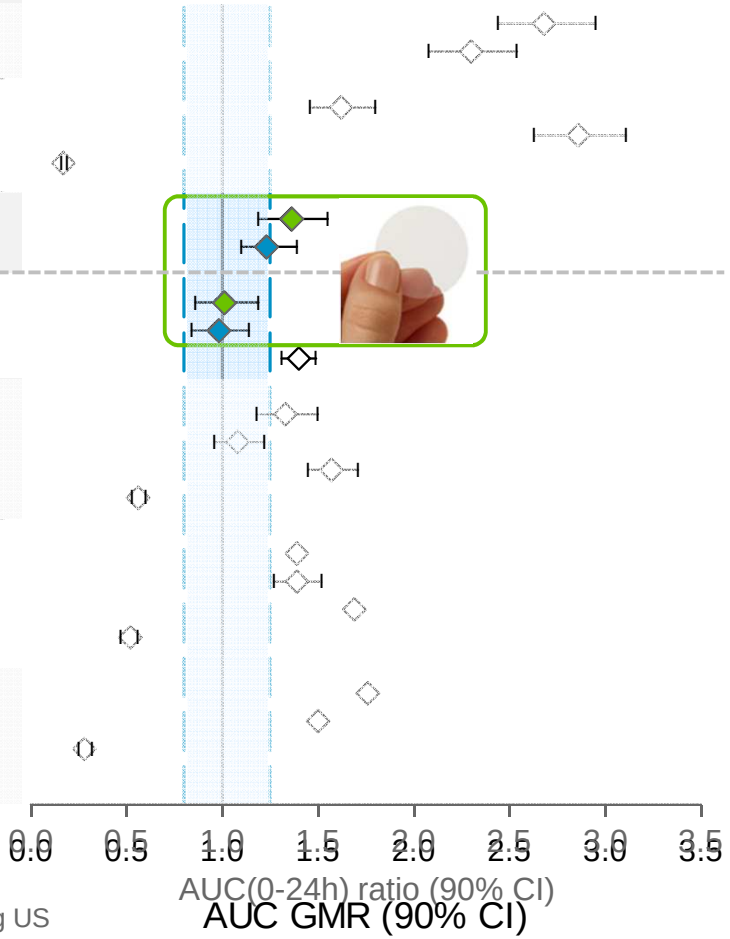


Winkler et. al. Eur J Drug Metab Pharmacokinet. 2014

CYP3A4 inhibition (HC as victim drug)

Effect of ERY and KTZ on apleek

Victim drug	Perpetrator drug
Drospirenone	Ketoconazole Ketoconazole
Dienogest	Erythromycin Ketoconazole Rifampicin
Gestodene*	Erythromycin Ketoconazole
Ethinylestradiol	Erythromycin Ketoconazole Ketoconazole
Estradiol (E2)	Erythromycin Ketoconazole Ketoconazole Rifampicin
Estrone (E2 metabolite)	Erythromycin Ketoconazole Ketoconazole Rifampicin
Estrone sulfate (E2 metabolite)	Erythromycin Ketoconazole Rifampicin



* Marketed in >70 countries world-wide, excluding US

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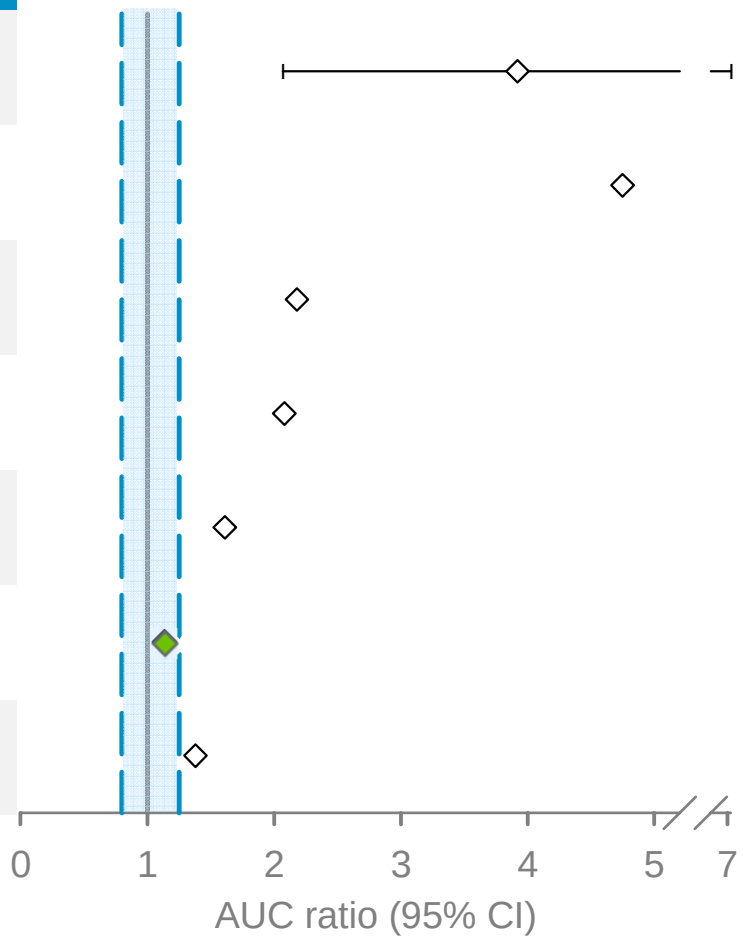
Clinical DDI experience with HCs (literature)

HCs as perpetrator drug (CYP1A2 substrates)

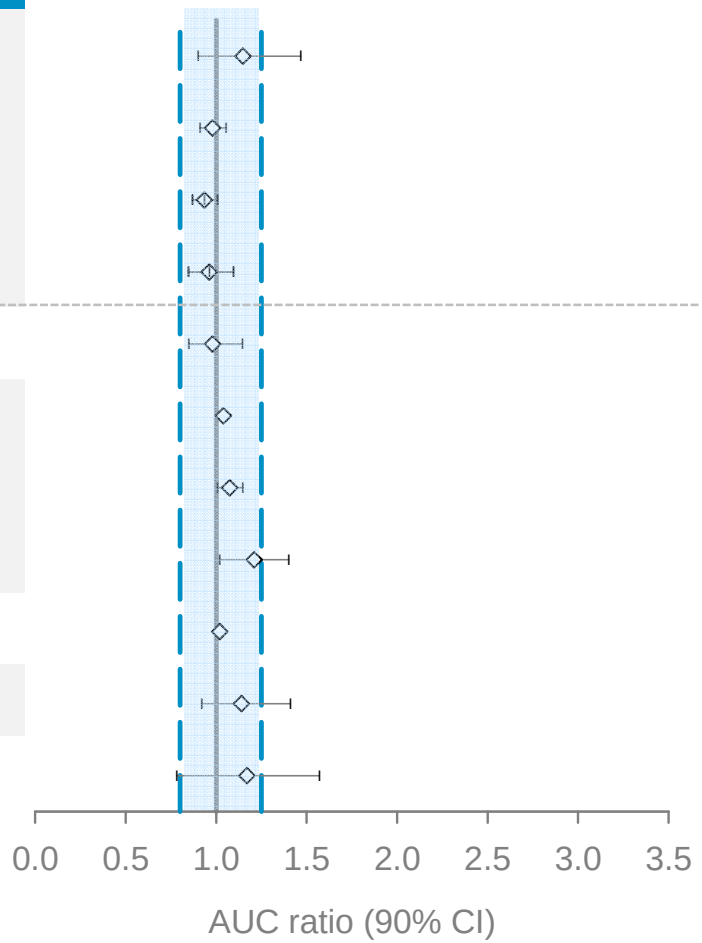
Perpetrator drug	Victim drug	Reference
EE / Gestodene	Tizanidine	Granfors et al. 2005
EE / diverse progestins	Melatonin	Hilli et al. 2008
EE / Gestodene	Caffeine	Balogh et al. 1995
EE / Levonorgestrel	Caffeine	Balogh et al. 1995
EE / Dienogest	Caffeine	Balogh et al. 1990
-- / Dienogest	Caffeine	Balogh et al. 1990
EE / unknown	Theophylline	Roberts et al. 1983



Clinical DDI experience with HCs

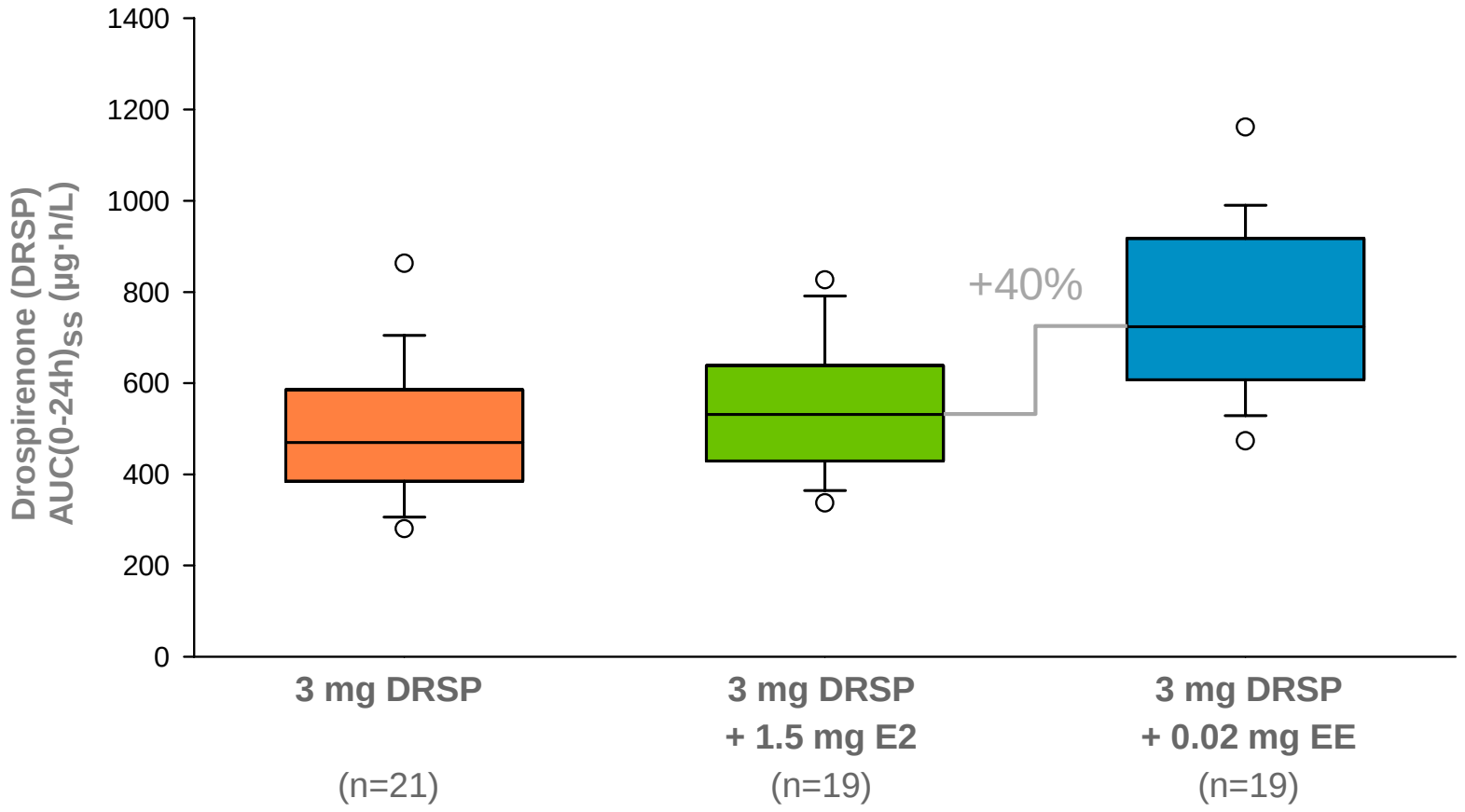
HCs as perpetrator drug (CYP3A4 substrates)

Perpetrator drug	Victim drug	Reference
Drospirenone	Simvastatin	
	Midazolam	
	5-OH Omeprazole*	
	Omeprazole-SO	
EE / Dienogest	Nifedipine	
EE / Gestodene	Nifedipine	
	Midazolam	
	Midazolam**	Palovaara et al. 2000
EE / Desogestrel	Nifedipine	
EE / Norgestrel	Midazolam**	Belle et al. 2002
EE / Levonorgestrel	Nifedipine	



* CYP2C19 substrate
** arithmetic mean ratio and 95% CI (all others geometric mean ratios)

Effect of EE and E2 on progestin PK



Box = 25th, 50th and 75th percentiles; error bars = 90th and 10th percentiles; open symbols = 5th and 95th percentiles

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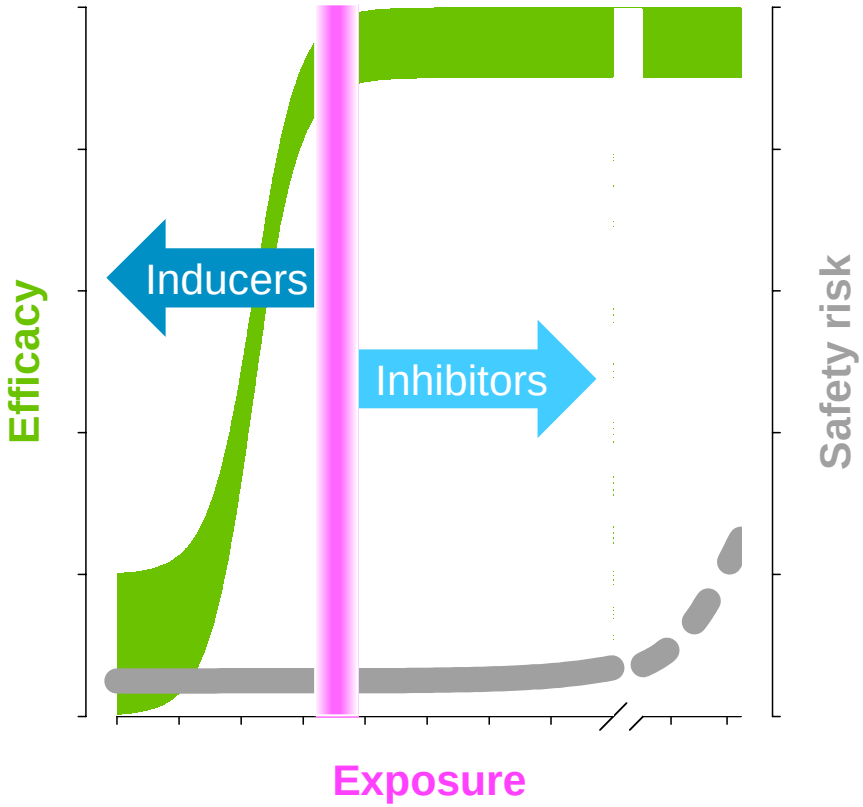
Clinical relevance of DDIs



DDI to be assessed in totality of data on PK/PD relationship regarding efficacy and safety, including considerations of overall variability, influence of intrinsic and other extrinsic factors

Science For A Better Life

Thank you!

Abbreviations

AKR	aldoketoreductase
AUC	area under the concentration vs. time curve from zero to infinity
AUC(0-24h)	AUC from zero to 24h
BID	bis in die (twice a day)
CI	confidence interval
CL	clearance
COC	combined oral contraceptive
CYP	cytochrome P450
DDI	drug drug interaction
DRSP	drospirenone
E2	estradiol
EE	ethinylestradiol
ERY	erythromycin
FDA	Food and Drug Administration
GSD	gestodene
HC	hormonal contraceptive
KTZ	ketoconazole
md	multiple dose
N	number
OH	hydroxy
PD	pharmacodynamics
PK	pharmacokinetics
PoC	proof of concept
QD	quaque die (once a day)
SO	sulfate
ss	steady state
SULT	sulfotransferase
UGT	uridine diphosphate glucuronosyltransferase
USAN	United States Adopted Name
US	United States
USPI	United States Product Insert

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