LESSONS FROM DEVELOPMENT: PERINDOPRIL / AMLODIPINE FIXED DOSE COMBINATION

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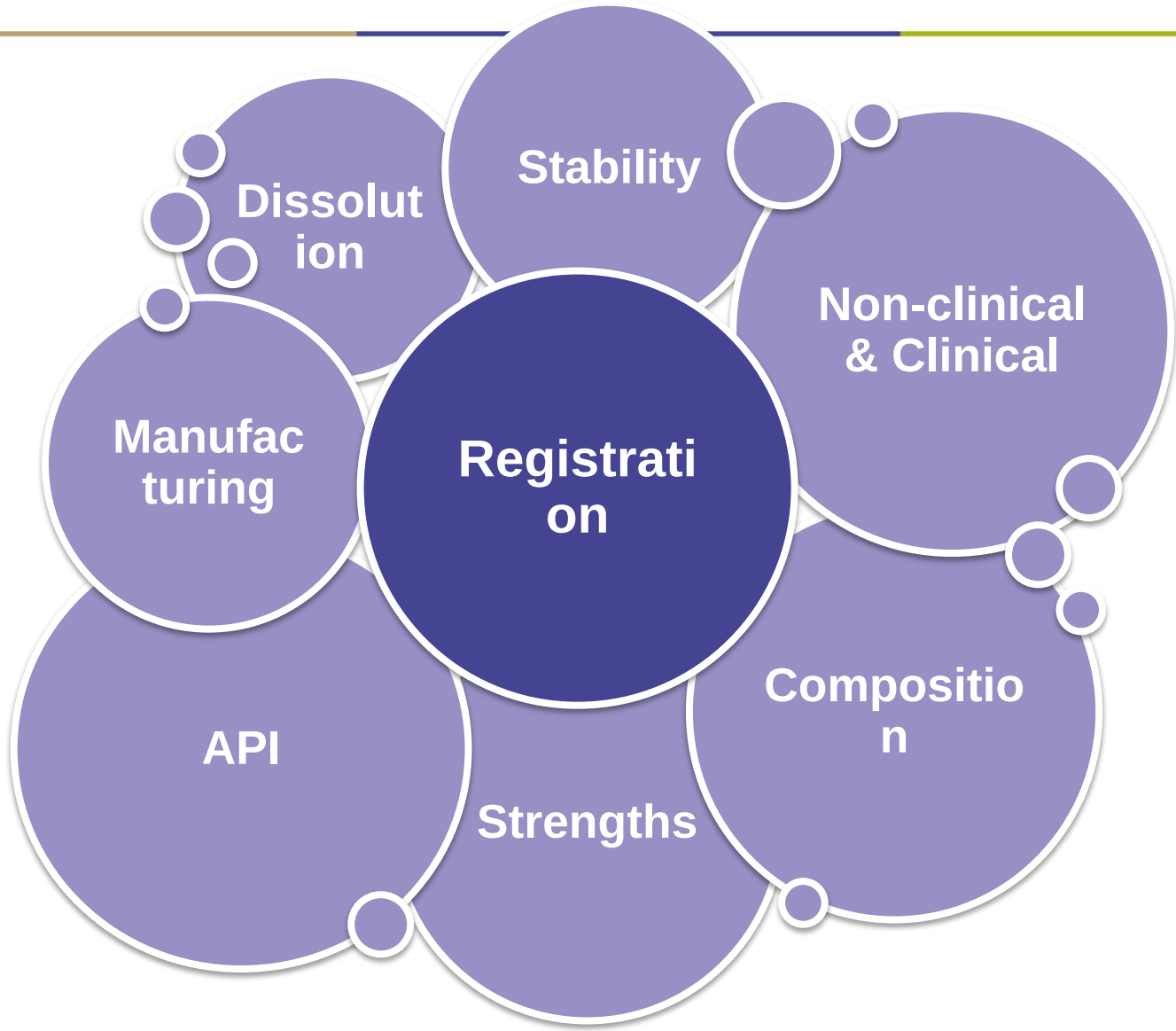
SANOFI GENERICS

PROJECT GOAL:
PERINDOPRIL / AMLODIPINE



REGISTRATION: 2001/83/EC

Article 10

1. … the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

Article 10b

…, the results of new pre-clinical tests or new clinical trials relating to that combination shall be provided in accordance with Article 8(3)(i), but it shall not be necessary to provide scientific references relating to each individual active substance.

Directive 2001/83/EC of the European Parliament of the Council of 6 November 2001 on the Community Code relating to Medicinal Product for Human Use.

CLINICAL DEVELOPMENT: INDICATION

2009 Guideline on Clinical Development of Fixed Combination

- ***First line therapy (initial combination therapy): patients receiving previously neither of the substances;***
- ***Second line therapy (add-on treatment): patients insufficiently responding to monocomponent(s);***
- ***Substitution therapy: patients adequately controlled with monocomponent(s);***

…clinical development should be performed accordingly.

Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/204/95 Rev.1)

INDICATION: SUBSTITUTION

2009 Guideline on Clinical Development of Fixed Combination

6.2.2. Pharmacokinetic studies:* (a) *bioequivalence between reference monocomponents and the fixed combination;* (b) *evaluate interactions between substances

6.3 Efficacy / Safety: combination in widespread use, a well founded bibliographical data analysis could be submitted.

6.4 Dosage strengths: doses used in broad clinical setting… comparability in the PK properties might be sufficient

6.5 Therapeutic trials: comparative pharmacokinetic and (in some cases) pharmacodynamic data are generally considered sufficient.

Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/204/95 Rev.1)

INDICATION: SUBSTITUTION

2010 Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension

1. All substances known and components in widespread use, … combination efficacious and safe and thus clinically useful.

- ***Well founded bibliographical data reduce clinical testing:***
- ***Comparative pharmacokinetic data are needed, … two components of the fixed combination do not affect each others pharmacokinetic patterns.***
- ***The pivotal data are the bioequivalence study showing bioequivalence to the components in free combination with the fixed dose.***

Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/238/1995/Rev.3)

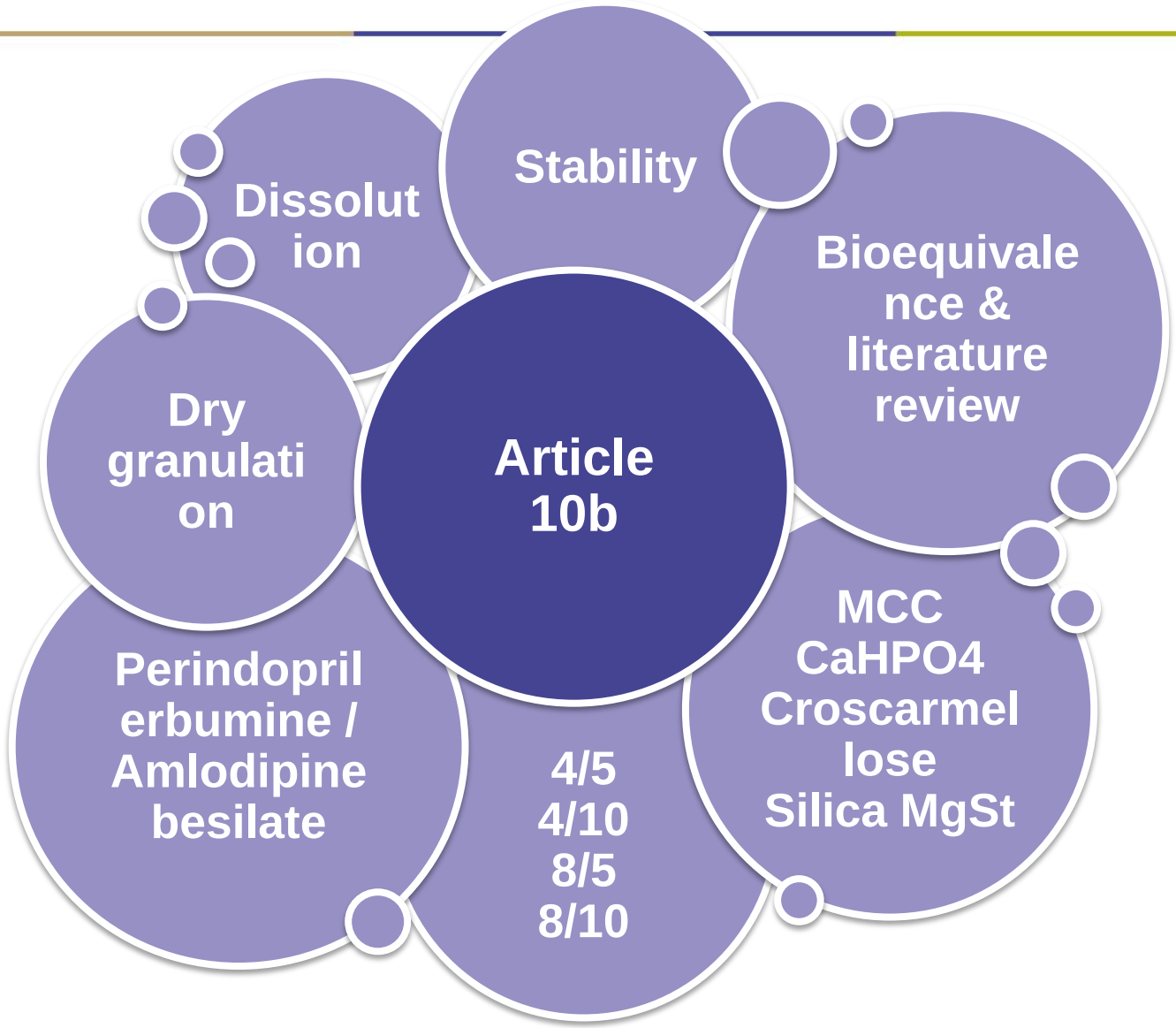
NON-CLINICAL DEVELOPMENT

2008 Guideline on the Non-clinical Development of Fixed Combinations of Medicinal Products

4.2.1 Fixed combination of compounds already approved as free combination therapy: When the fixed combination under development includes compounds for which there is sufficiently documented human experience of their individual and combined use, safety studies in animals are in general not required.

Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005)

PROJECT GOAL:
PERINDOPRIL / AMLODIPINE



PERINDOPRIL / AMLODIPINE: LESSONS

Lesson 1: Composition

- **API (perindopril erbumine vs. arginine)**
- **Formulation composition**

Lesson 2: Bioequivalence study

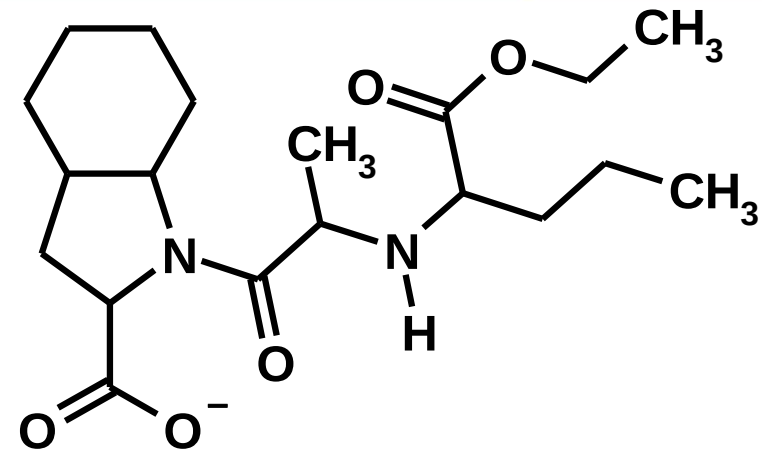
- **Metabolite vs. parent drug for perindopril**
- **Sampling design**
- **Truncated AUC**

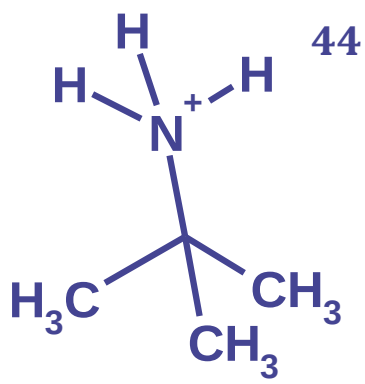
Lesson 3: Registration / Deficiency & Responses

- **Independent data / data exclusivity**
- **Evidence that each component contributes efficacy**
- **Evidence of widespread use and safety**
- **Pharmacokinetic interaction**

(1) ERBUMINE VS. ARGININE

Perindopril

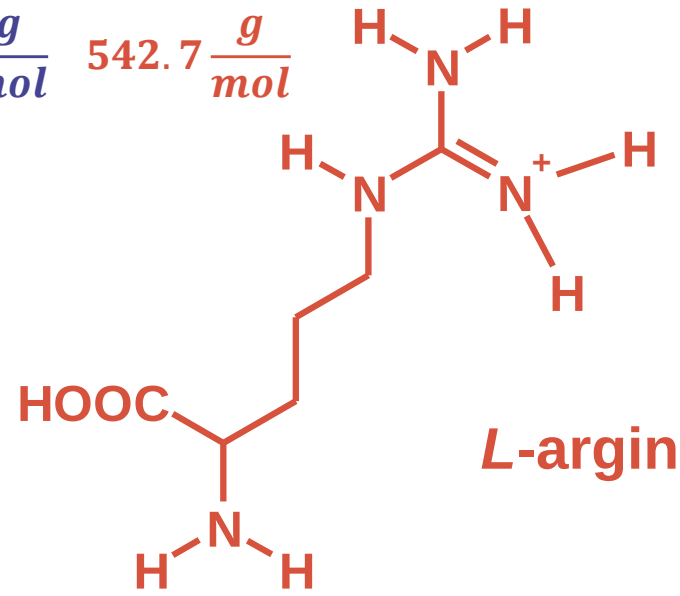




Tert-butylamine

$441.6 \frac{g}{mol}$

$542.7 \frac{g}{mol}$



L-arginine

ERBUMINE VERSUS ARGININE

- *Tert*-butylamine (erbumine) salt developed originally (Servier)
- Erbumine replaced by arginine as being **more stable** (the product can be distributed to climatic zones III and IV without the need for specific packaging)
- Molecular weight (Mw) of arginine salt ~23% higher than erbumine salt (542.7 vs. 441.6 g/mol): 8 mg of perindopril erbumine **equimolar** to 10 mg of perindopril arginine
- Erbumine salt shown **bioequivalent** to arginine salt (an open-label, randomized, two-period, crossover, pharmacokinetic study involving 36 healthy male volunteers)

Telejko, E (2007). Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril, *Current Medical Research and Opinion* 23: 953–960

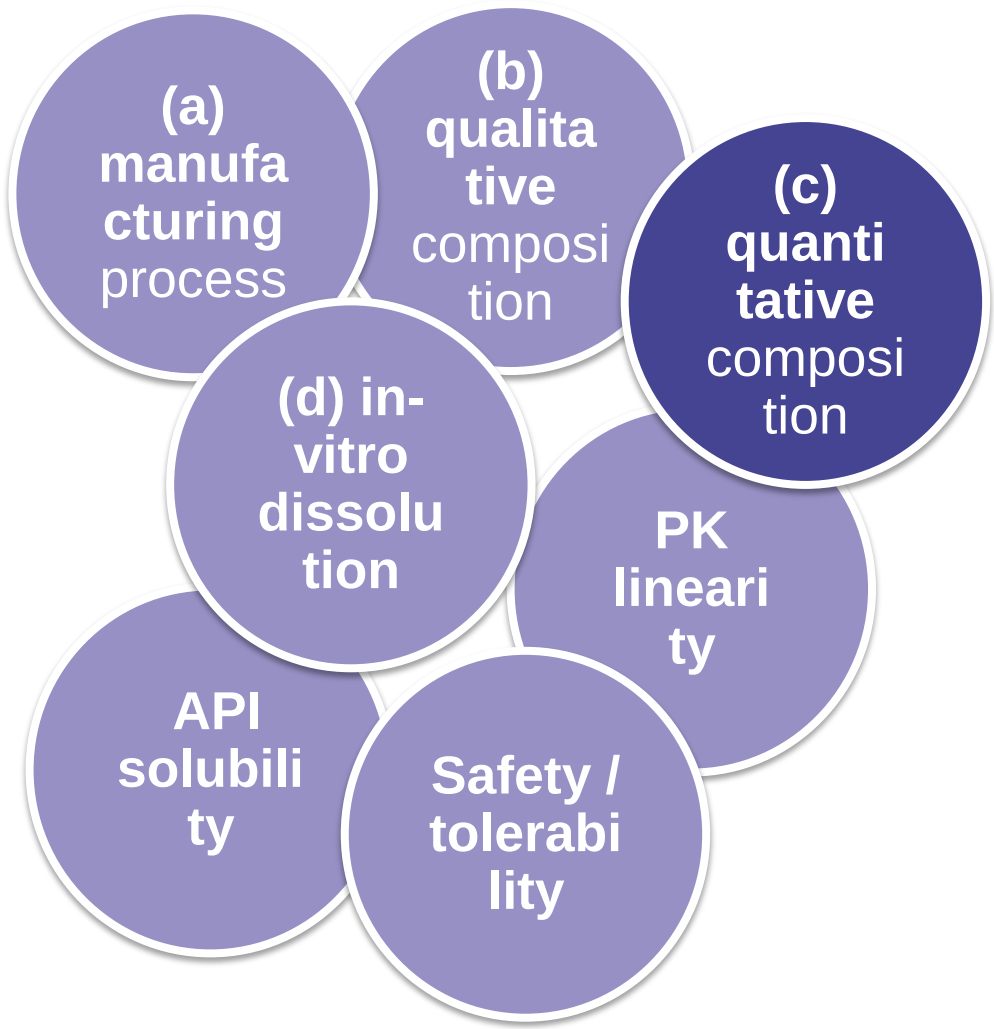
- **Patent** limitation (expiry 2023) for arginine: use erbumine salt

COMPOSITION AND BIOWAIVER

EMA Guideline on Investigation of bioequivalence

If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths and other product related issues...

Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)



COMPOSITION: PROPORTIONAL

General biowaiver criteria: (c) the composition of strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths.

Fixed combinations … conditions regarding proportional composition should be fulfilled for all active substances ... When considering amount of each API, other API can be considered as excipients.

Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

COMPOSITION: PROPORTIONAL?

Example: combination (mixed) tablet (mg)				
P (mg)	4	4	8	8
A (mg)[1)]	5	10	5	10
Excipient 1	80	80	160	160
Excipient 2	80	160	80	160
Total (mg)	169	254	253	338
[1)] amount of base considered for didactic reasons only				

COMPOSITION: PROPORTIONAL?

Ratio(s) excipient(s) vs. P (mg)				
P (mg)	4 mg	4 mg	8 mg	8 mg
A	1.25	2.5	0.625	1.25
Excipient 1	20	20	20	20
Excipient 2	20	40	10	20

Ratio(s) excipient(s) vs. A (mg)				
P	0.8	0.4	1.6	0.8
A (mg)	5 mg	10 mg	5 mg	10 mg
Excipient 1	16	8	32	16
Excipient 2	16	16	16	16

non-proportional

COMPOSITION: <5% RULE

If there is some deviation from quantitative proportional composition, condition (c) is still considered fulfilled if: (i.) the amount of active substance is less than 5% of the tablet core weight … , and (ii.) or (iii.) … apply to the strength used in the bioequivalence study and the strength for which waiver is considered.

Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

COMPOSITION: <5% RULE

(i.) and (ii.) same tablet core weight

P (mg)	4	4	8	8
A (mg)	5	10	5	10
Excipient 1	130	130	130	130
Excipient 2	150	150	150	150
Total (mg)	289	294	293	298

(i.) and (iii.) same total tablet weight

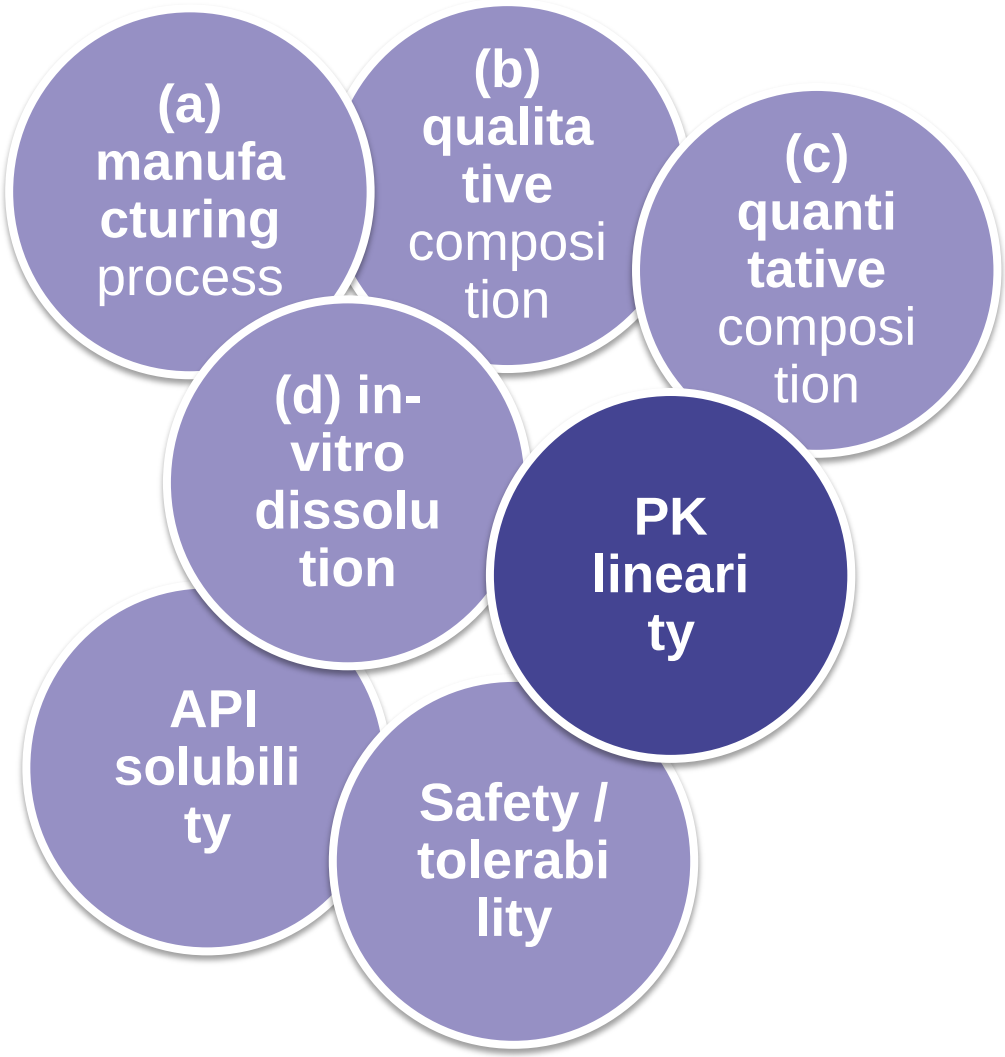
P (mg)	4	4	8	8
A (mg)	5	10	5	10
Filler	121	116	117	112
Excipient 2	150	150	150	150
Total (mg)	280	280	280	280

COMPOSITION: FINAL

P in mg (% API)	4 (2.86)	4 (1.43)	8 (2.86)	8 (2.86)
A in mg (% API)	6.934 (4.95)	13.868 (4.95)	6.934 (2.48)	13.868 (4.95)

[1)]Cellulose, microcrystalline; excipients: calcium hydrogen phophate dihydrate; croscarmellose sodium; Colloidal silica anhydrous; magnesium stearate

GENERAL BIOWAIVER CRITERIA



(2) DESIGN FACTORS

Pharmacokinetic properties

- **Linearity (strength to be selected for in-vivo)**
- **C_{max} (bioanalytical method LOQ)**
- **T_{max} (sampling)**
- **Metabolism (parent vs. metabolite; bioanalytical method)**
- **Elimination half-life $T_{1/2}$ (wash-out, sampling, AUC_{0-t} AUC_{0-72})**

Variability of pharmacokinetics

- **2-way cross-over or replicate design**
- **Sample size / power**

Other design factors

- **Healthy volunteers or patients**
- **Fed or fasting …**

PHARMACOKINETICS

Basic characteristics		
Properties	**Perindopril**	**Amlodipine**
BCS	III	III[1]
PK	linear	linear
Metabolite	active[2]	inactive
$T_{1/2}$ (hr)	~1	35-50
T_{max}[3] (hr)	0.67 (0.33-1.50)	7.00 (5.00-10.00)
CV_w[4] (%)	23 (19-29)	11 (7-14)

Source data: SmPC Coversyl Arginine / Istin; TMAX in-house data; (1) absolute bioavailability 64-80%; (2) perindoprilat; (3) median (min-max); (4) pooled within-subject variability for CMAX metric (min-max); ***abbreviations:*** BCS Biopharmaceutics Classification System; PK pharmacokinetics

STANDARD DESIGN

If two formulations are compared, a randomized, two-period, two-sequence single dose cross-over design is recommended.

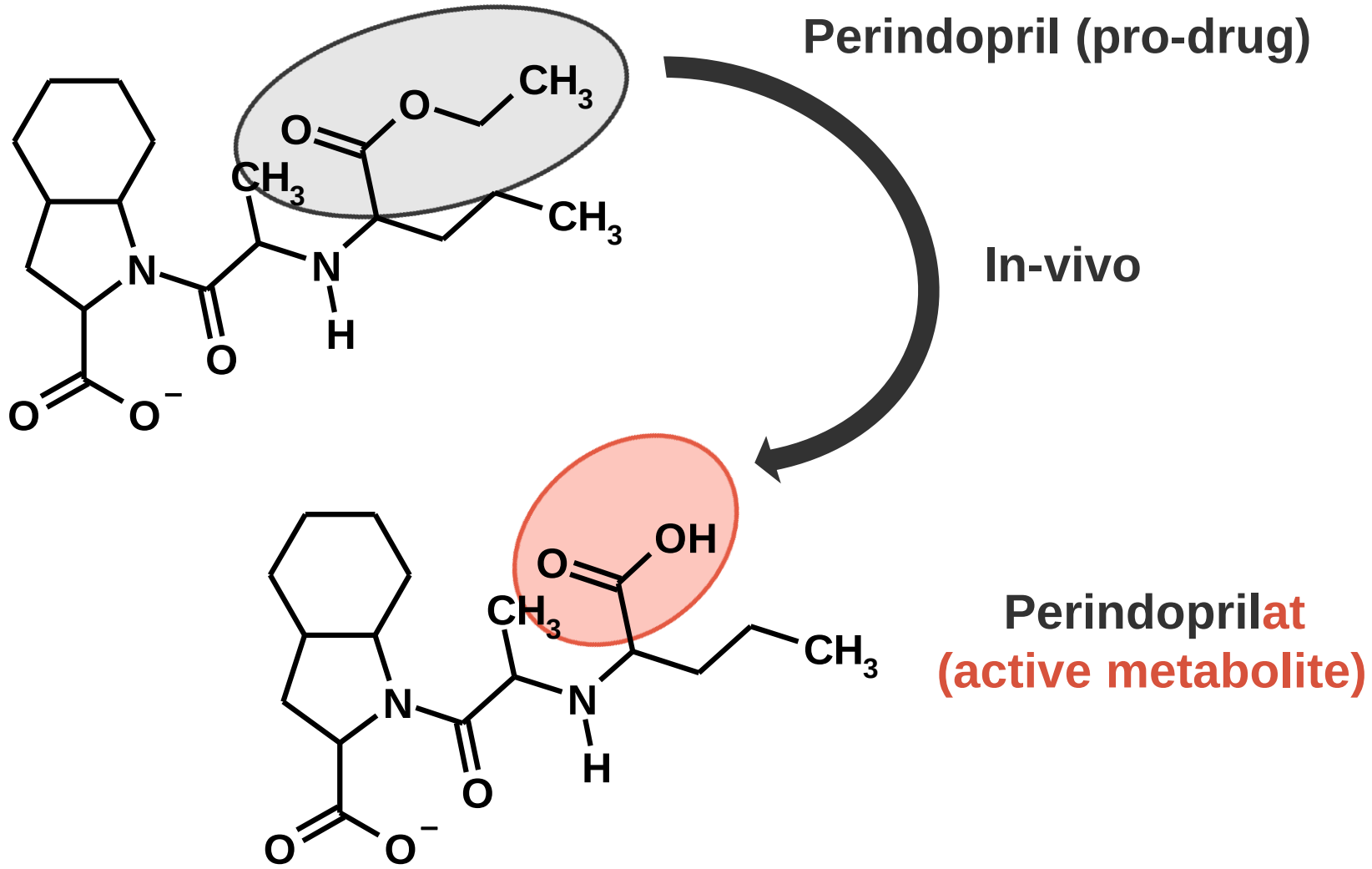
Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

2x2x2[(a)] cross-over design [(a)] formulation x sequence x period		
Sequence	**Period 1**	**Period 2**
1	Reference	Test
2	Test	Reference

Test: Perindopril / Amlodipine 8/10 mg fixed dose combination

Reference: Coversyl Arginine 10 mg co-administered with Istin 10 mg

PARENT AND METABOLITE



PARENT AND METABOLITE

EU: EMA Guideline on Investigation of Bioequivalence

In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound.

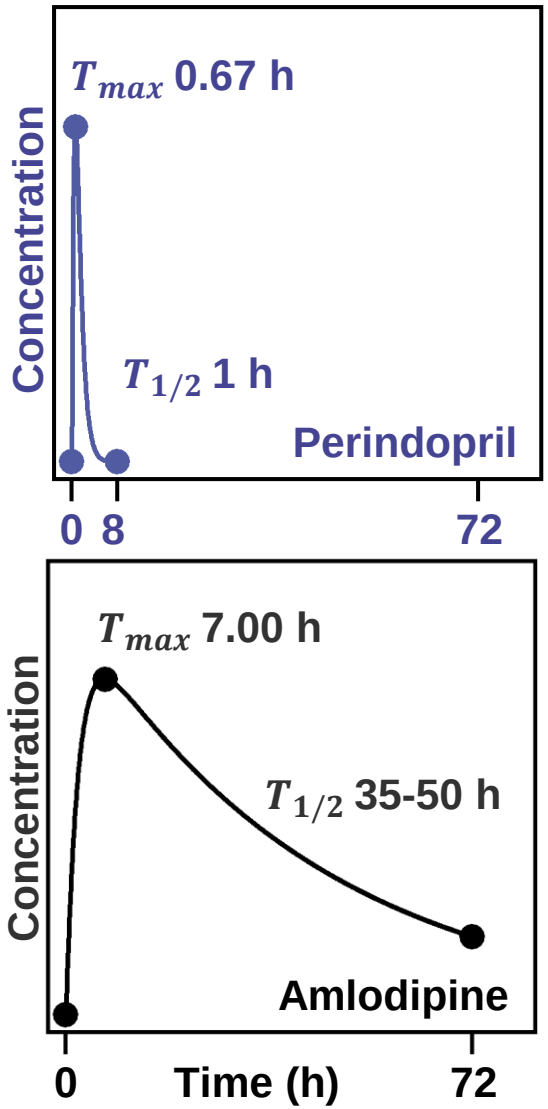
Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

US: FDA Bioequivalence Recommendations for Perindopril

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

FDA Bioequivalence Recommendations for Specific Products: Guidance on Perindopril erbumine; Recommended 5/2008

SAMPLING / BLOOD DRAWS

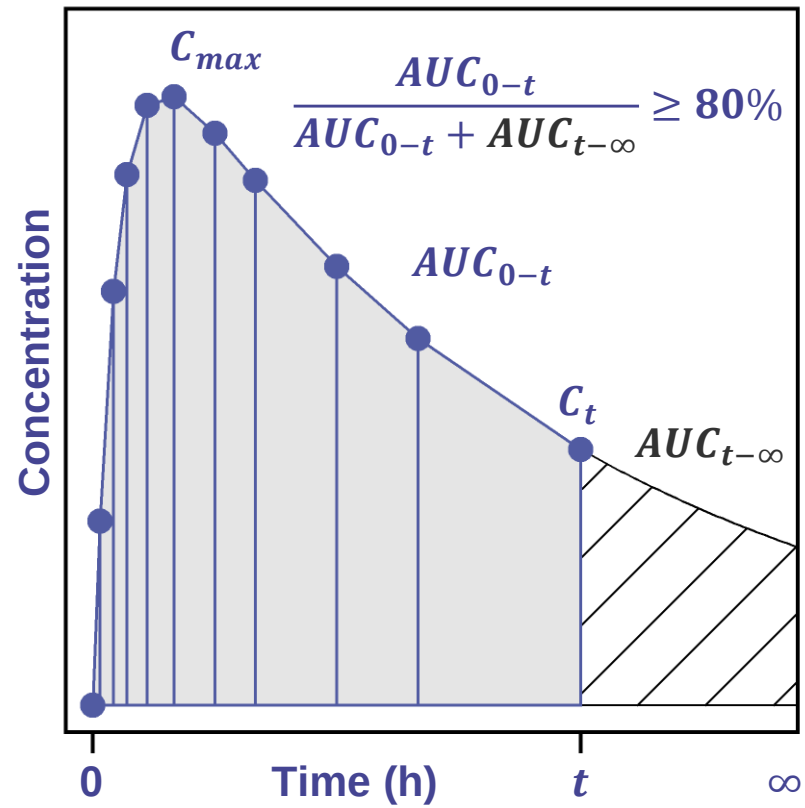


Perindopril (h)	Amlodipine (h)
0 (pre-dose)	0 (pre-dose)
0.167;0.333;0.5; 0.667;0.833;1; 1.25;1.5	
2;2.5	2
3;3.5	3
4;4.5	4
5;6;7;8	5;6;7;8
	9;10;11;12;14; 16;24;48;72
=19 samples	=17 samples

PHARMACOKINETIC METRICS

Primary PK metrics	
C_{max} AUC_{0-t}	C_{max} AUC_{0-72}

AUC truncated at 72 hours may be used as an alternative to AUC(0-t) for comparison of extent of exposure… …, and where the concentration at 72h is quantifiable, AUC(0-∞) and residual area do not need to be reported; …

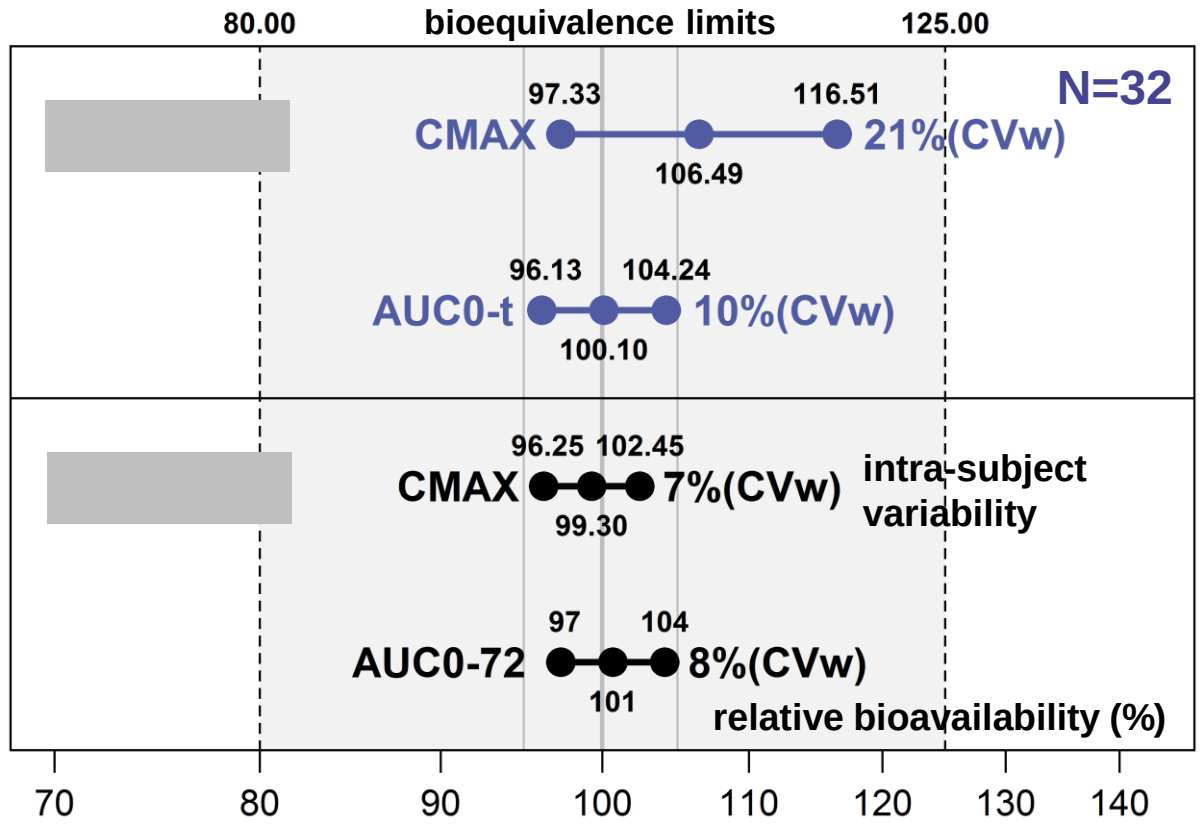


Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)

BEQ STUDY DESIGN: SUMMARY

- 2x2x2 cross-over study (in fasting conditions)
- 34 healthy volunteers
- Test: Perindopril / Amlodipine 8/10 mg
- Reference: Coversyl Arginine 10 mg + Istin 10 mg
- 28 blood draws per subject per period
- Analytes: perindopril and amlodipine
- PK-metrics: C_{max}, AUC_{0-t} [redacted], AUC_{0-72} [redacted]
- Acceptance criteria: 80.00-125.00%
- Wash-out: 21 days

BIOEQUIVALENCE: TEST VS. REFERENCE



90% confidence intervals for Perindopril erbumine /Amlodipine 8/10 mg vs. Coversyl Arginine 10 mg co-administered with Istin 10 mg; study under fasting conditions

(3) REGISTRATION: ASSESSMENT

V.3 Clinical aspects

Potential serious risk to public health: product non-approvable

- **Efficacy and safety data used to support application may be under protection / breach of data exclusivity**
- **Evidence that each component contributes efficacy to the combination to be provided**
- **Evidence of widespread use and safety for the combination (e.g. co-prescription data) to be provided**

Points for clarification

- **Potential for pharmacokinetic interaction not adequately described: data to be provided**

REGISTRATION: ASSESSMENT

Clinical aspects

Potential serious risk to public health

… in view of application, according to Article 10b of Directive 2001/83/EU own clinical data should be submitted. Bioequivalence study is not relevant and … only as data supportive. …, literature data is not sufficient to justify authorisation. The applicant is asked to provide adequate results of own clinical studies to demonstrate the efficacy and safety of this fixed combination.

STATUS: PROJECT ECG

QUESTIONS & ANSWERS

Questions

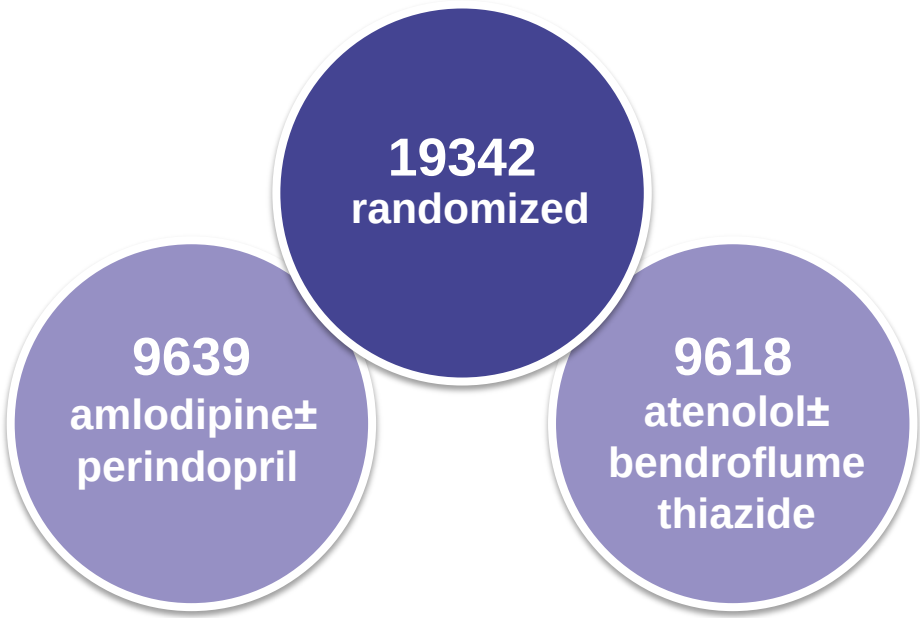
- Efficacy and safety data under protection / data exclusivity
- Evidence that each component contributes efficacy
- Evidence of widespread use and safety
- Potential for pharmacokinetic interaction

Answers

- Review published evidence: data under protection?
- Large clinical outcome study: benefit of the combination
- Collect co-prescription data and review PSUR
- Conduct pharmacokinetic interaction trial

Anglo-Scandinavian ascot-BPLA
Cardiac Outcomes Trial
Blood Pressure Lowering Arm

- **Antihypertensive patients**
- **40-79 years**
- **3 cardiovascular risk factors:**
  - Left-ventricular hypertrophy
  - Type 2 diabetes
  - Peripheral arterial disease
  - Previous stroke or ischaemic attack
  - Male sex
  - Age 55 year or older
  - Microalbuminuria or proteinuria
  - Smoking
  - Ratio total cholesterol to HDL 6 and higer
  - Family history of premature coronary heart disease



ASCOT-BPLA: MAIN RESULTS

	Effect of treatment / events			
	Endpoint	Amlodipine ±P (n=9639)	Atenolol ±B (n=9618)	Reduction vs. A±B
I	MI / CHD(1)	429	474	10%
II	Mortality(2)	738	820	11%*
II	CV mortality	263	342	24%**
II	Stroke(3)	327	422	23%***
III	Onset DM(4)	567	799	30%***
Post-hoc	CV+MI/stroke(5)	796	937	60%***

Treatment groups: Amlodipine / Perindopril vs. Atenolol / Bendroflumethiazide;
(1) non-fatal myocardial infarction (including silent)+fatal CHD; (2) all-cause mortality; (3) fatal and non-fatal stroke; (4) onset of diabetes mellitus; (5) cardiovascular death+myocardial infarction+stroke; significance: <0.05 *, <0.01 **, <0.001 ***

I primary; II secondary; III tertiary endpoints

Dahlöf et al., 2005

ASCOT-BPLA: EFFICACY / SAFETY PROOF

- This trial does not bring evidence of contribution of each monocomponent, …
- Amlodipine adding Perindopril is better than Atenonol adding Bendroflumethiazide in terms of reducing the incidence of all types of CV events and all-cause mortality, and in terms of risk of subsequent new-onset diabetes
- The study was supported mainly by Pfizer, New York, NY, USA. Funding was also provided by Servier Research Group, Paris, France
- Previous MAA referencing to ASCOT-BPLA were approved

Dahlöf et al. (2005). Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. Lancet 366: 895-906

CO-PRESCRIPTION DATA

Patients on perindopril and amlodipine (vs. on perindopril alone)			
Country	**2011[a]**	**2012[c]**	**2013[e]**
[redacted]	14%	15%	16%
	2%	7%	2%
	6%	6%	4%
	31%[b]		
		18%[d]	
Average	11%		

(a) Q2-Q4 / 2011; (b) Q1-Q4 / 2011; (c) Q1-Q4 / 2012;
(d) 11 / 2011 -10 / 2012; (e) Q1 / 2013

PHARMACOKINETIC INTERACTION

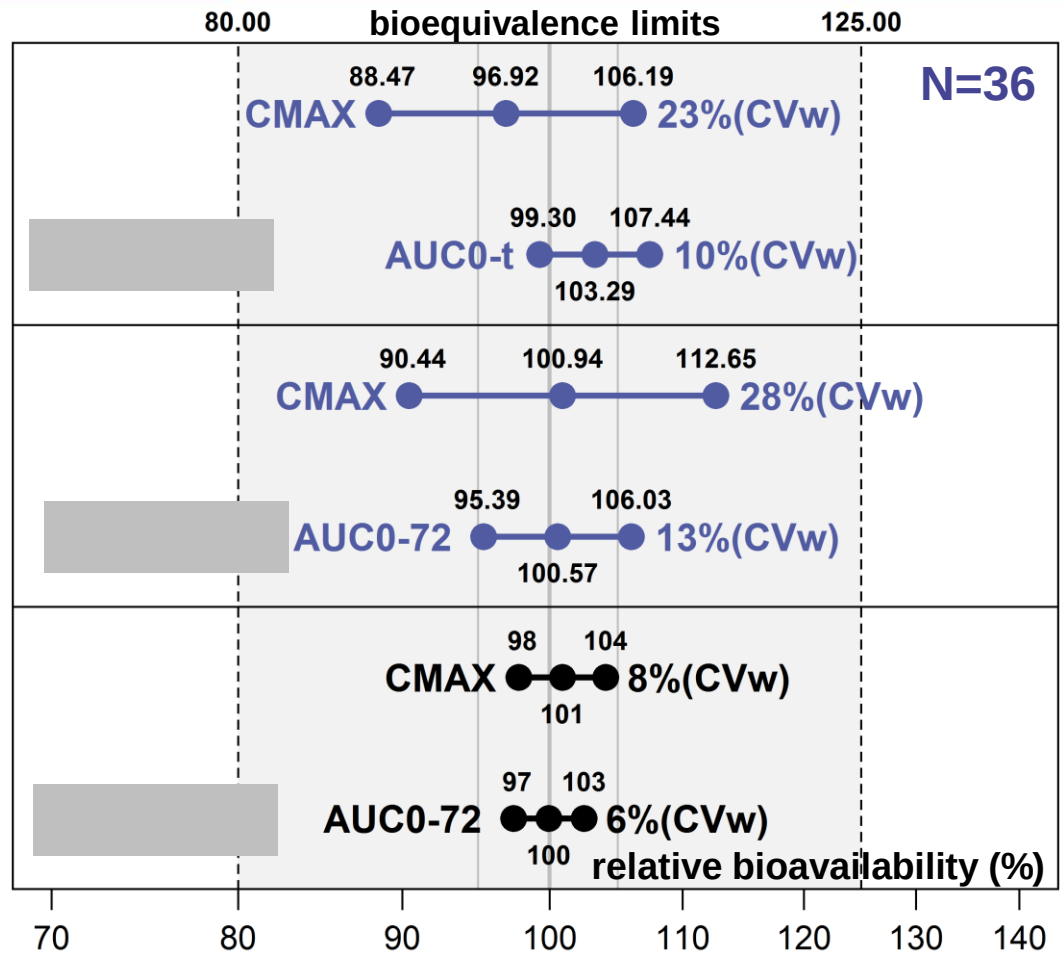
3x6x3[(a)] Latin square (cross-over) design [(a)]formulation x sequence x period			
Sequence	**Period 1**	**Period 2**	**Period 3**
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	B	A	C
6	C	B	A

A: Coversyl Arginine 10 mg co-administered with Istin 10 mg

B: Istin 10 mg (amlodipine besilate)

C: Coversyl Arginine 10 mg (perindopril arginine)

PHARMACOKINETIC INTERACTION



90% confidence intervals for Coversyl Arginine 10 mg or Istin 10 mg vs. Coversyl Arginine 10 mg co-administered with Istin 10 mg

ASSESSOR'S COMMENTS: [redacted]

- **Efficacy and safety data under protection / data exclusivity**

Data exclusivity of several literature references has been re-evaluated. It is agreed … literature references … are unlikely under data exclusivity. However the responsibility in this issue still lies with [redacted] … clinical trial ASCOT-BPLA ... considered as appropriate proof of … efficacy. [redacted] applicant's argumentation. Issue resolved.

- **Evidence of widespread use and safety**
- **Evidence that each component contributes efficacy**

Literature references … in combination with co-prescription data are considered as acceptable rationale for substitution indication of fixed dose combination. Issue resolved.

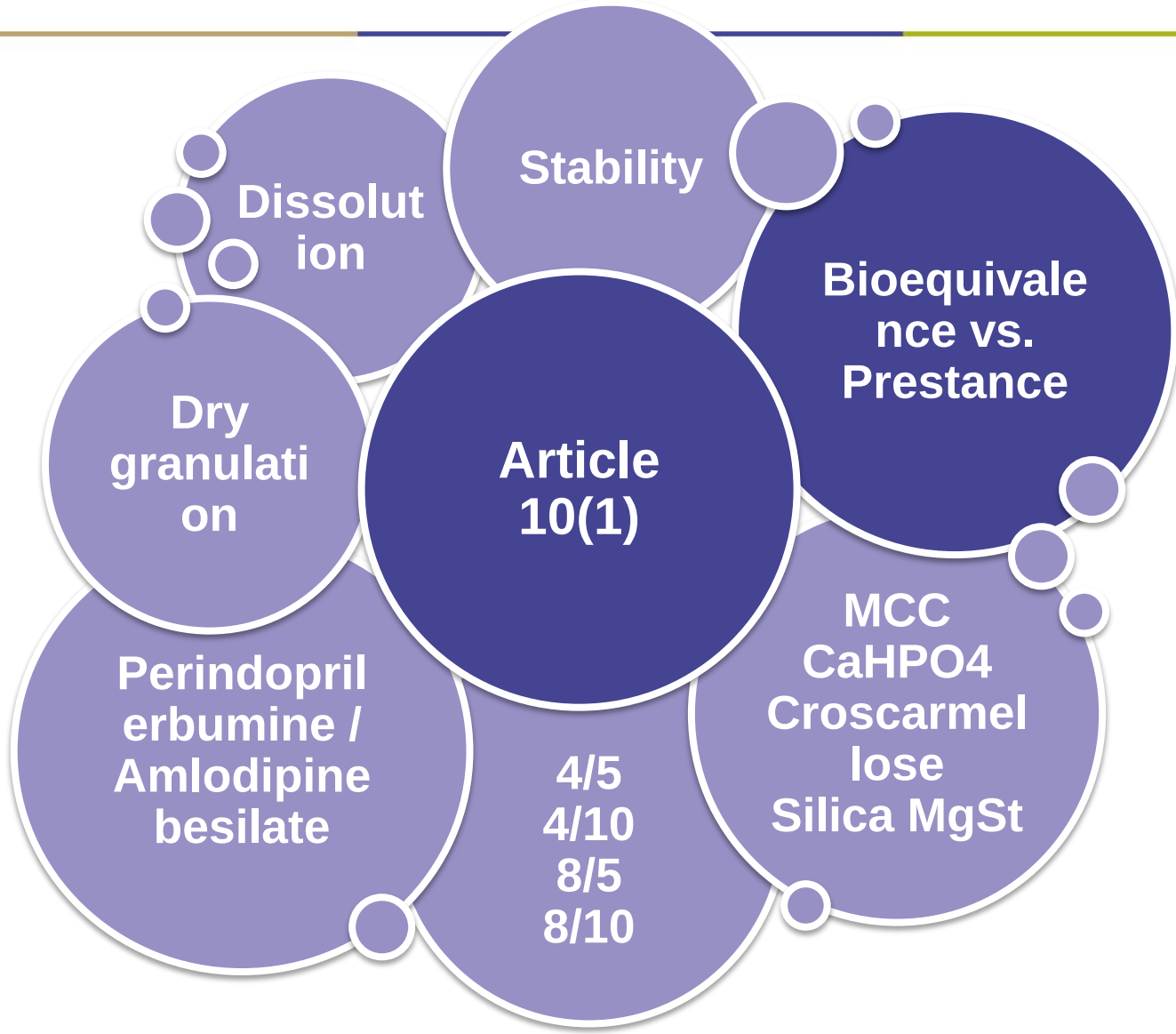
ASSESSOR‘S COMMENTS: D120

- **Potential for pharmacokinetic interaction**

Interaction study design is appropriate as well as analytical method used. This study suggests there are no pharmacokinetic interactions between amlodipine, perindopril and perindoprilat following a single dose administration under fasting condition. Issue resolved.

D203 end of procedure:

PROJECT GOAL:
GX PERINDOPRIL / AMLODIPINE



ESSENTIAL LEARINGS

Lesson 1: Composition

- **API: concept of different salts**
- **Formulation composition: homothetic and <5% rule**

Lesson 2: Bioequivalence study

- **Metabolite vs. parent drug: regulatory requirements**
- **Sampling design: individual PK properties**
- **Truncated AUC: molecules with long half-life**

Lesson 3: Registration / Deficiency & Responses

- **Independent data / data exclusivity**
- **Evidence that each component contributes efficacy**
- **Evidence of widespread use and safety**
- **Pharmacokinetic interaction**

EMA GUIDELINE: IN REVISION

2015 Draft Guideline on Clinical Development of Fixed Combination Medicinal Products: substitution indication

- ***Combination is pharmacologically plausible and based on valid therapeutic principles***
- ***The population in need of the FDC is clearly identified***
- ***Each component contributes to efficacy and safety and/or enhances PK/PD of active substance(s): evidence across all strengths in non-responders / 3-arm study (AB vs. A vs. B)***
- ***Drug-drug interaction studies***
- ***Evidence of documented clinical use of the combination***
- ***Bioequivalence FDC vs. mono-components taken simultaneously***
- ***Favorable benefit-risk balance***