A European Regulator's perspective on Fixed Dose Combinations

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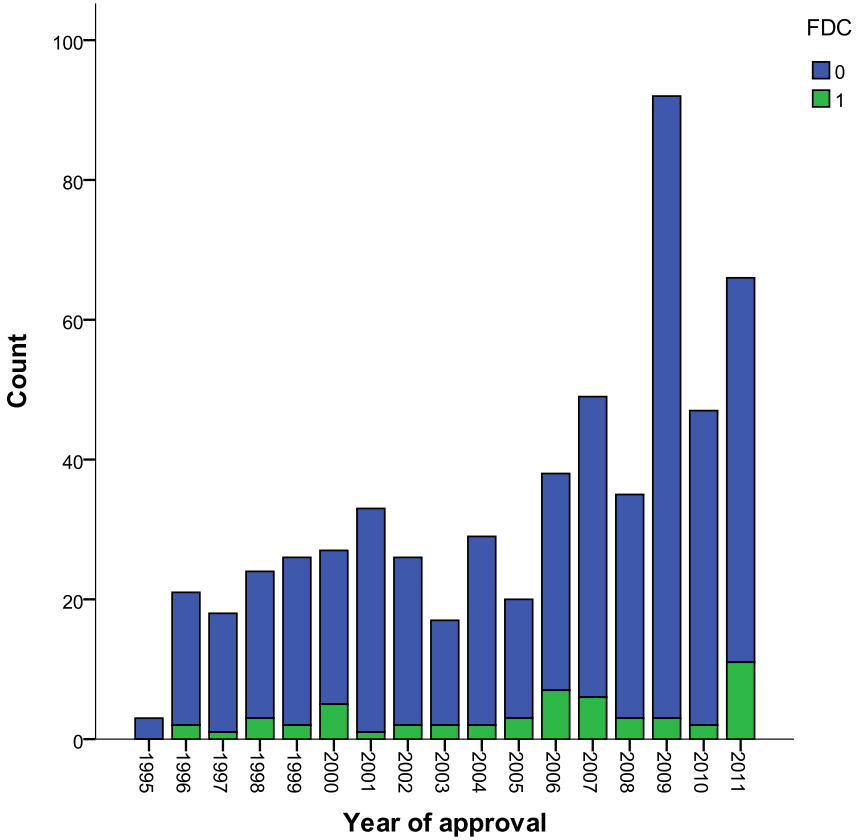
Guidance documents

- Fixed Combination Medicinal Products [CHMP/EWP/240/95 Rev. 1, Sept 2009]
- Q&A on clinical development of combinations belonging to different therapeutic classes for prevention and treatment of CV diseases [CHMP/EWP/191583/05]

- Guideline on clinical investigation of medicinal products in the treatment of hypertension [CPMP/EWP/238/95 Rev. 3]
- Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus [CHMP/EWP/1080/00 Rev. 1]

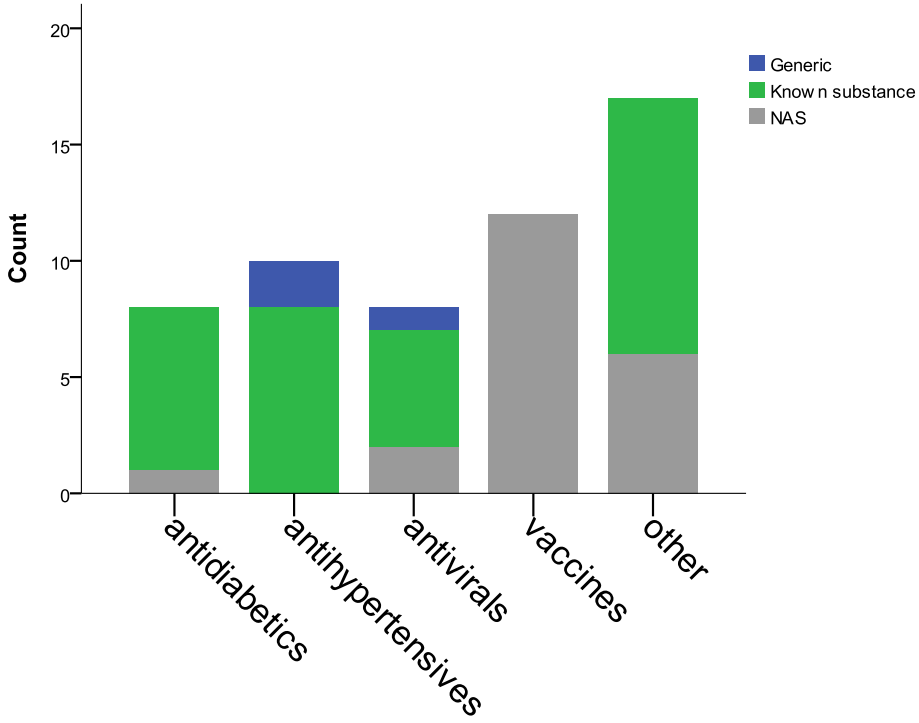
How many FDC's in Europe?

Centrally Approved Products 1996 - 2011



Incl. generics, vaccines

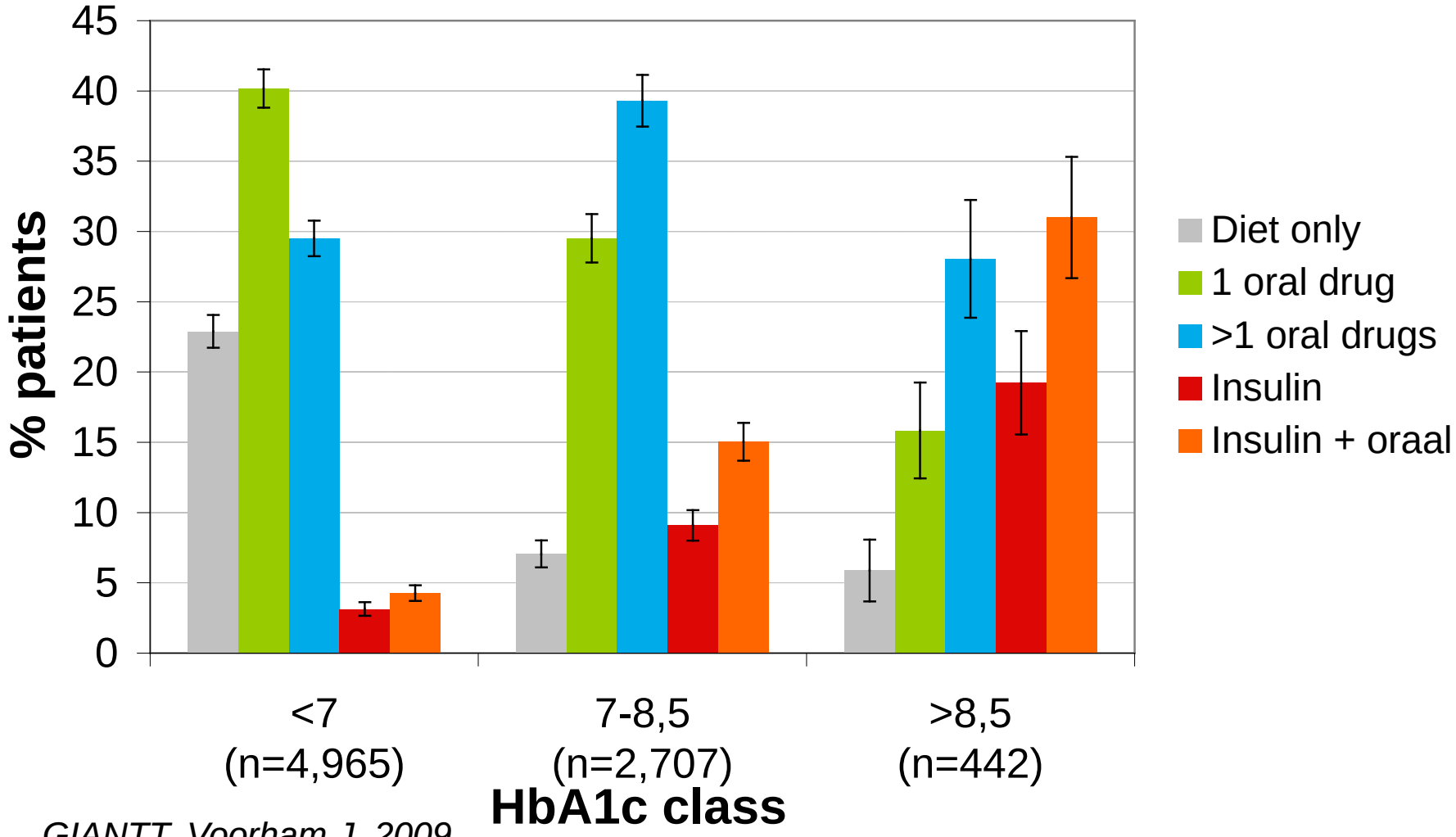
FDC (n=55) Therapeutic group



Rationale for these most common FDCs

- Vaccines – patient convenience / logistics
- HIV/AIDS – improving compliance with multi-drug regimen, substitution indication -> primarily BE, combined therapy standard of care, and PK booster
- T2DM – often non-response, metformin only drug with established efficacy on hard endpoints – cornerstone of therapy (and many FDCs)
- Hypertension
  - Over 60% require two or more drugs to reach BP targets (ALHATT)
  - Certain combinations are synergistic (thiazides + ACEi/ARB, CCB + BB, CCB + ACEi/ARB)
  - *Combined initial treatment in high risk patients!?*

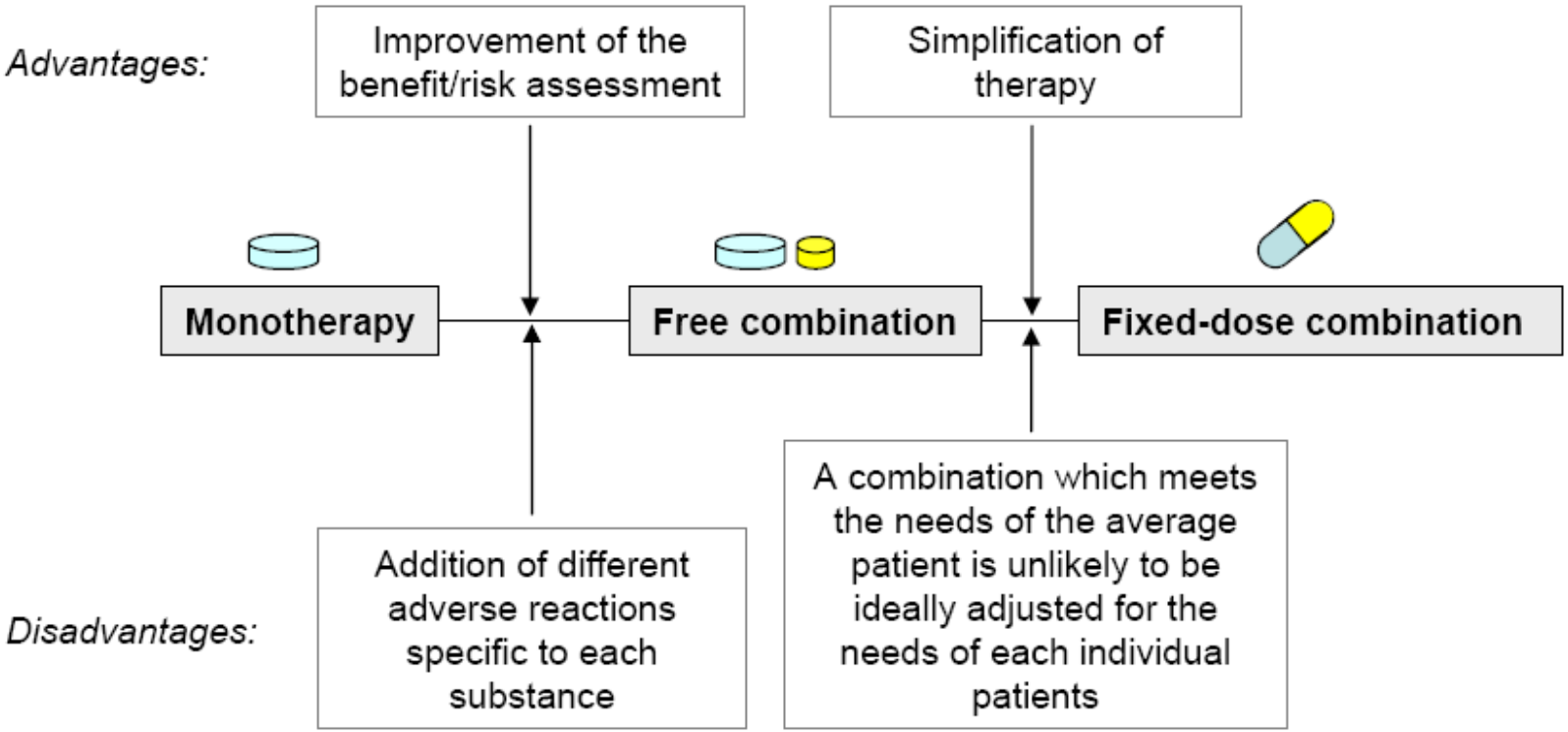
Non-response + multi drug therapy in T2DM



GIANTT, Voorham J. 2009

Rationale Fixed Dose Guideline

'valid therapeutic principle'



Improvement of benefit/risk

- Addition or potentiation of therapeutic effect

  Similar *efficacy* than monotherapy at higher dose with **better** *safety* profile

  or

  More *efficacious* than monotherapy and **acceptable** *safety* profile

- Counteracting adverse reaction (serious or commonly occurring) of one substance by another

Simplification of therapy

- 'Substitution indication'
  - Patient convenience…and possibly improved compliance, which is particular important in field of HIV, TB because of resistance
    - Mondero et al. 2011 Int J Tuberc Lung Dis: TB FDC review: similar efficacy well demonstrated, but only one study addresses drug resistance -> recommend to use based on *user-friendliness*, low costs, *logistical advantages*
    - But…seldom proven
    - "..the least frequent [reason] and even challenging to achieve with regulators."
      [Company comment to draft guideline]

‘General Rules’

- “..the choice of each substance in the FDC as well as the whole concept on which the fixed combination is based have to be fully justified.”
  - Mechanism of action, PK and treatment recommendations
- Duration of action of monocomponents similar (except e.g. absorption enhancers, or successive actions)
- Each substance documented therapeutic contribution to FDC <-> ‘poly pill’

Not accepted are:

- Give unpleasant adverse events to prevent abuse
- Narrow therapeutic index drugs

Clinical development

Depends on:

- Whether one or more active substances are well-known or not yet authorised (for the intended claim)
- Intended use, first or second line therapy of patients inadequately controlled on monotherapy
- *Intended indication, single disease, two closely related diseases (or symptoms), 'substitution' indication*

Type of active substances:

- Extent of efficacy & safety studies depends on
  - FDC corresponds closely to combinations in widespread use
    - Forego dose finding
    - Bibliographicly supported
  - FDC is essentially new (AS not usually combined, unusual doses or one active is NAS)
    - Data needed similar to NAS (for first or second line indication)
    - Existing experience with compounds

Intended indication

Q&A Fixed Combinations belonging to different therapeutic classes in the field of CV treatment and prevention

- Rationale – Cardiovascular treatment guidelines – managing various risk factors simultaneously: hypertension, diabetes, lipids, arterial thrombosis
- Two scenarios
  - 'Substitution' indication
    - A) components administered at same dose interval
      - BE study – possibly food interaction, dose proportionality and SAFETY if necessary
    - B) same interval but different dose timing
      - PK as above and PD study to show different timing is not relevant (non-inferiority) and SAFETY if necessary
    - C) different dose interval, e.g. BD to OD– different dose per intake
      - New dose regimen for one component – thus therapeutic equivalence of new dosing schedule compared to old, PD data (non-inferiority), when higher dose than SAFETY
  - Wider indication
    - Entirely new indication (e.g. prevention of CV events)
    - New development – outcome studies?

Dosage strengths & treatment regimen

- Dosage of components must be such that, *combination* is *safe & effective* in *sizeable* target population with a B/R equal or better than of single component
- Minimal effective dose, usual effective dose -> multilevel factorial design
- *When FDC intended to simultaneously relieve different symptoms of disease, each substance at commonly effective dose*
- When doses are similar to broad clinical use of combination of components, PK data may suffice

Therapeutic Trials

- Confirmatory clinical trials:
  parallel group comparisons to individual substances, and possibly placebo/reference treatment
  - For first line therapy – study design depends on clinical practice and treatment recommendations in each therapeutic field
  - For second line therapy – trial in non-responders to *optimally* dosed monotherapy is recommended
  - Study design should follow disease specific guidelines
    - patient population, incl. severity of disease,
    - primary and secondary endpoints,
    - study duration
  - For 'substitution' comparative PK and (some cases) PD data are generally considered sufficient!
- Mostly concern one disease

PK & PD studies

- PD: the rationale for the FDC
  - Dose range – factorial design
- PK:
  i. Generic of existing FDC – BA&BE guideline / BCS biowaiver possible
  ii. 'Substitution' indication or known active substances not used as free combination -> demonstrate BE of FDC with free combination
  iii. (one of the) active substances is a new AS then full PK characterisation

  Of note: for ii + iii determine *interaction [booster!]*,

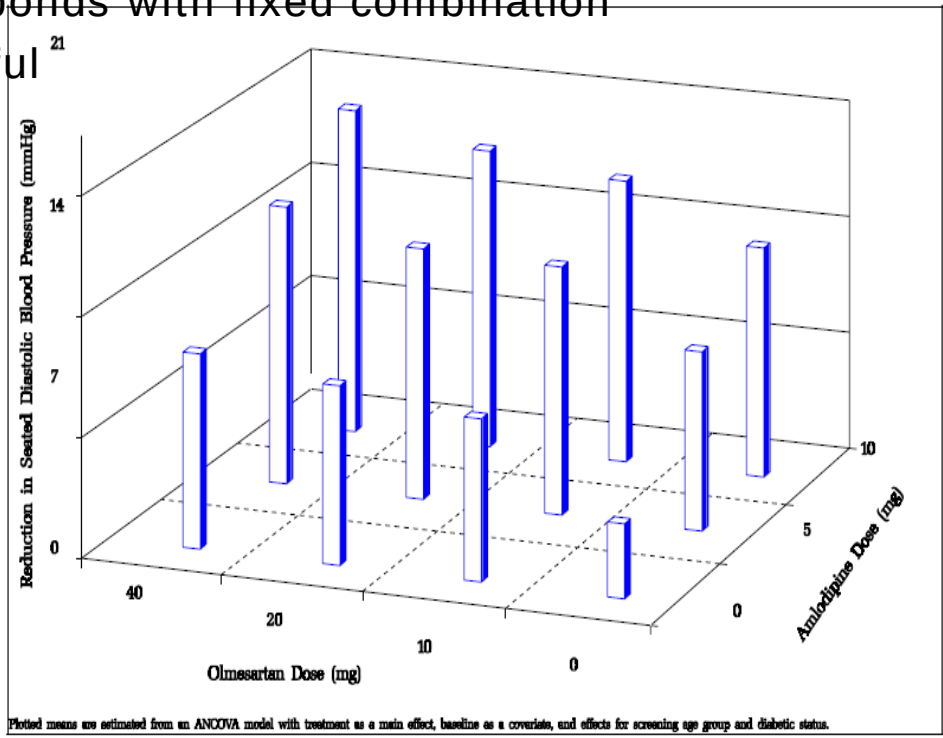
  Biowaiver for other FDC strengths (see BA&BE guideline), food interaction required with modified release

Safety aspects

- Follow NfG for specific targeted disaese(s)
- New safety data:
  - 'Substitution' indication: literature
  - Otherwise, self-standing safety database
  - Rationale for bridging safety data are:
    - Knowledge of active substances in claimed indication , but if one NAS in FDC -> full dossier
    - Proposed dosing schedule: changes in dose or posology regimen may lead to tolerability issues: specifically for switchers
    - Impact PK / PD interactions for safety
    - Existing recommendations on specific safety issues (special populations (elderly, renally impaired), cardiac repolarisation -> thorough QT study)
    - Long-term data (or justify lack)

Example - antihypertensives

- Requirements
  - Combination mechanistically plausible –> additive BP lowering effects or reduction of ADRs
  - Efficacy & safety of individual components proven (clin trials)
  - Individual dosage ratio corresponds with fixed combination
  - Joint application is clinical useful
- Dose finding
  - **Factorial design** (incl. placebo)

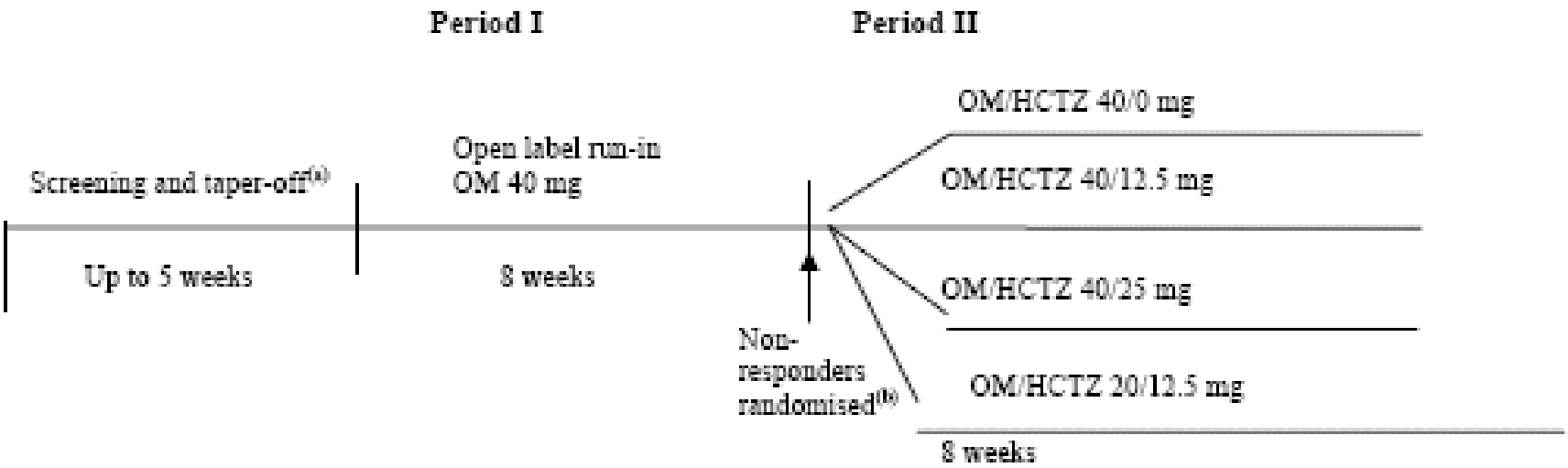


Antihypertensive FDCs (II)

- Second line
  - Add-on therapy in non-responders
    - Statistically and clinically relevant added BP lowering
    - Single components not forced to max dose, but compare with maintenance dose (clinical practice)
    - Mean beneficial effect on supine/sitting SBP and DBP ***plus*** preferentially proportion responders
    - Sufficient time to reach targets
  - Parallel group comparison (supportive)
  - In case of e.g. combining two diuretics (one K^+sparing) a clinically beneficially safety profile has to be formally shown

Add on design (FDC with multiple dose strenghts)

Figure 1: Study CS866-CM-B-E301 Schematic Flow Diagram of the Treatment Arms

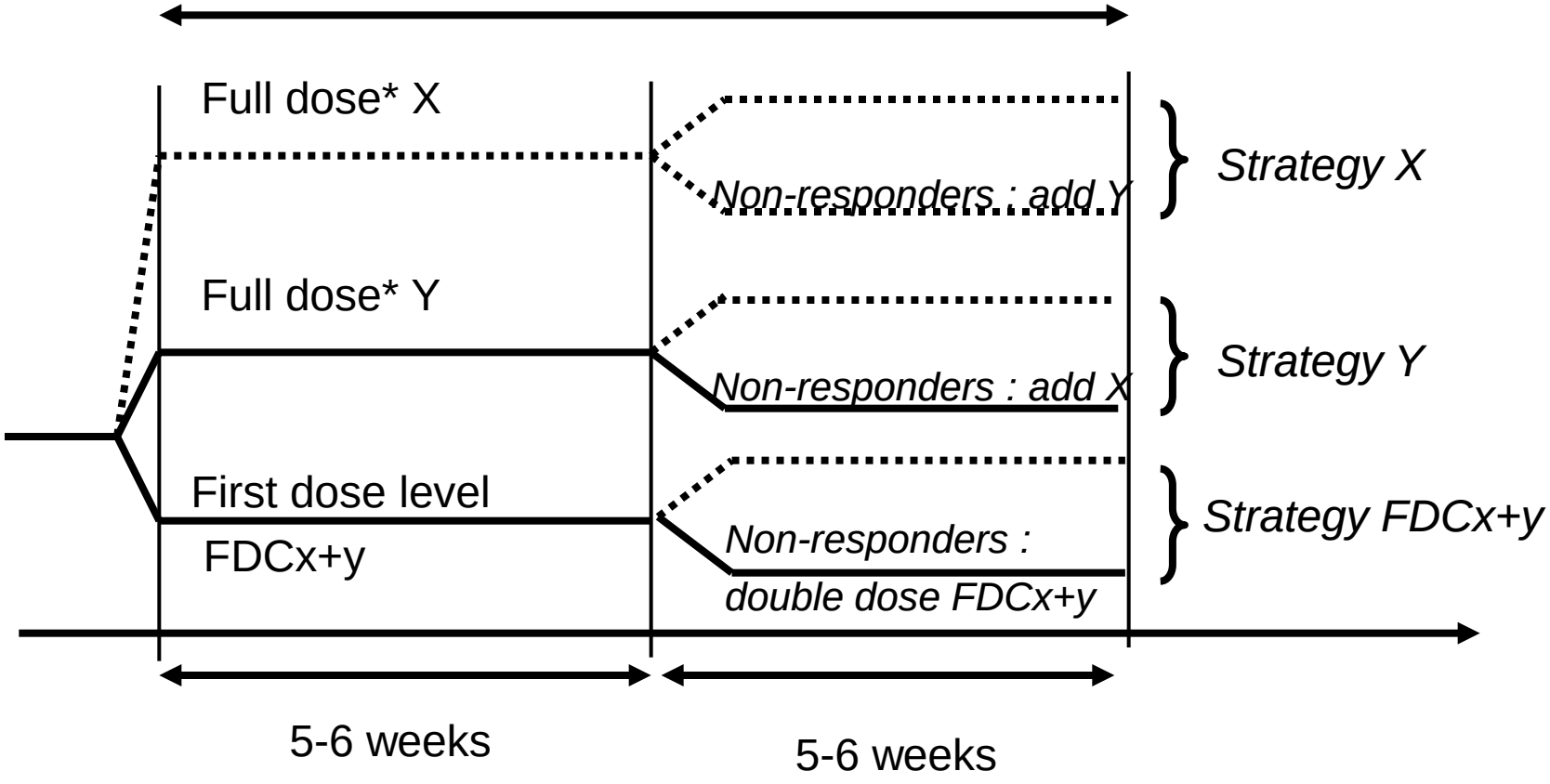


First line indications

- Sub therapeutic doses
  - Each component should contribute
    - E.g. >2mmHg DBP↓ + more responders than placebo
    - At least *statistically* superior to monocomponent at low dose
  - Fewer ADRs than monocomponents in lowest approved dose
    - Similar BP lowering
    - Trend towards better safety and response rate than on lowest approved dose
- Therapeutic dose
  - All substances well known: single confirmatory trial -> *more rapid BP lowering*
  - CAVE: orthostatic hypotension, steal effect (renal dysfunction & cerebral hypoperfusion), first dose hypotension, and unnecessary drug use
  - Appropriate population: moderate to severe hypertension, high CV risk

Confirmatory trial

Primary efficacy analysis: responders, BP reduction [**non-inferior**]



Secondary efficacy analysis: time until achieving target BP level [**superior**]

** Uptitration may be necessary*

Conclusion

- No CV preventive FDC currently approved
  - Limited experience through Scientific Advice
- For any FDC
  - Demonstrated added value of each component
  - ‘substitution’ indication may be way out, but demonstration of bioequivalence can be challenging
- Regulators struggle with CV outcome studies – with multiple (>3) components