Outstanding development and registration of Dasatinib VAM

Bio-bridges

September 22, 2022

ZENTIVA

WHAT IS WRONG with DASATINIB?

SPRYCEL is indicated for the treatment of adult patients with Ph+ chronic myelogenous leukaemia (CML)…

„Therapy should be initiated by a physician experienced in the diagnosis and treatment of patients with leukaemia.“

Special warnings and precautions for use

- The concomitant use of dasatinib and a histamine-2 (H2) antagonist, proton pump inhibitor, or …may reduce the exposure to dasatinib. Thus, H2 antagonists and PPI inhibitors are not recommended, and aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib.

*How many pages has Sprycel´s SmPC?

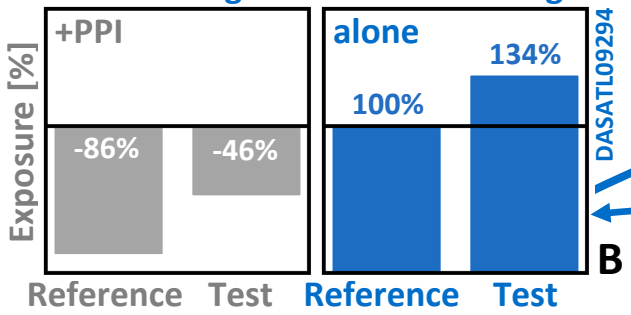
ANSWERS

despite the warning more than 20% of patients with CML are given PPI´s patients are not achieving predictable effective plasma concentrations 31

DASATINIB ZENTIVA: DEVELOPENT PATHWAY

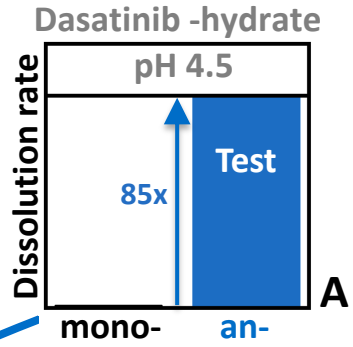
Proof-of-concept

Test 140 mg & Reference 140 mg

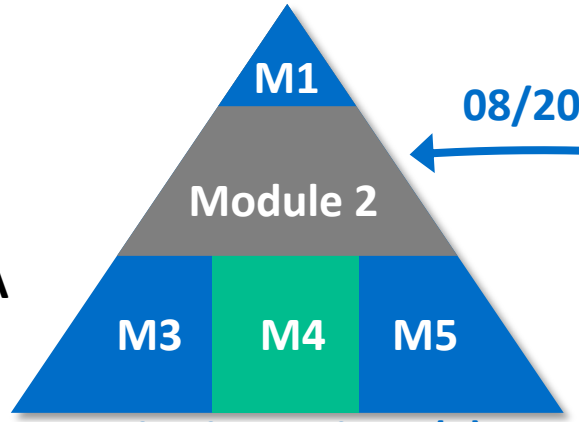


09/2018

New product: suprabiovailability & lower pH sensitivity

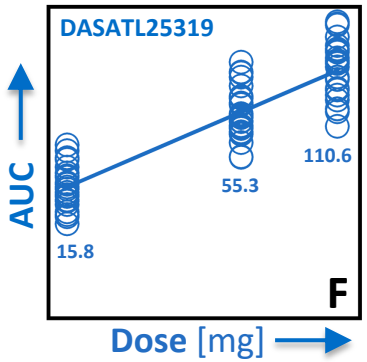


08/2020



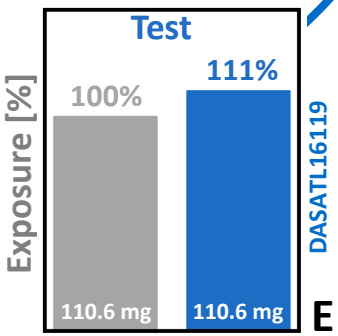
Hybrid: Article 10(3)

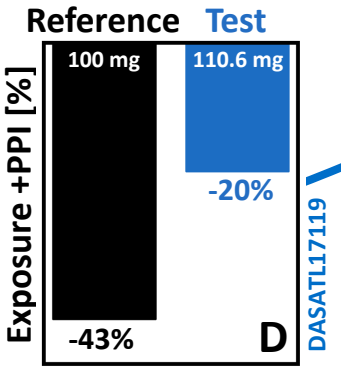
Dose-proportionality



01/2020

Food effect



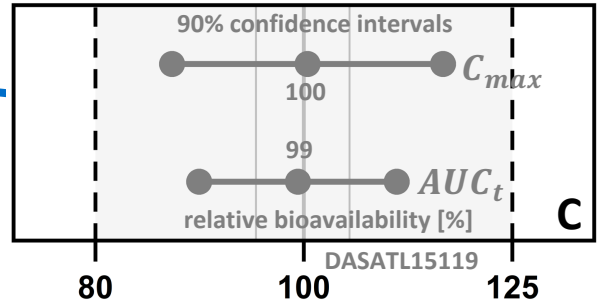


PPI-interaction

staggered administration

Pivotal fasting bioequivalence

Test 110.6 mg vs. Reference 140 mg



Dose reduction: -21%

08/2019

Scientific advice

05/2019

DASATINIB VAM ZENTIVA: REGISTRATION

QUESTIONS: CMDh and CHMP REFERRAL

(1) **The applicant is asked to justify the choice of the legal basis and why a clinical trial to demonstrate its own efficacy and safety has not been conducted.**

(2) **The applicant should discuss the data from the fed and fasted study and justify how efficacy and safety data obtained with the reference product may be extrapolated to their product.**

(3) **The applicant is asked to discuss and justify the claim of allowing administration of PPI and the clinical need for concomitant administration of PPI and dasatinib should be included in the discussion.**

(4) **… the applicant is asked to further discuss the benefit risk ratio in the view of the potential risk for medication error balanced against any potential advantages the product under evaluation might have over the product …**

QUESTION 1: CHOICE OF LEGAL BASIS

Product	Label claim (mg)					
Reference	140	100	80	70	50	20
Test	110.6	79.0	63.2	55.3	39.5	15.8

Notice to Applicants (Volume 2A, Chapter 1, 2019). Hybrid application for products: (1) where the strict definition of a 'generic medicinal product' is not met; (2) where bioavailability studies cannot be used to demonstrate bioequivalence; (3) where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference product.

Article 10(3) justified.

28.11.2001 Official Journal of the European Communities L 311/67

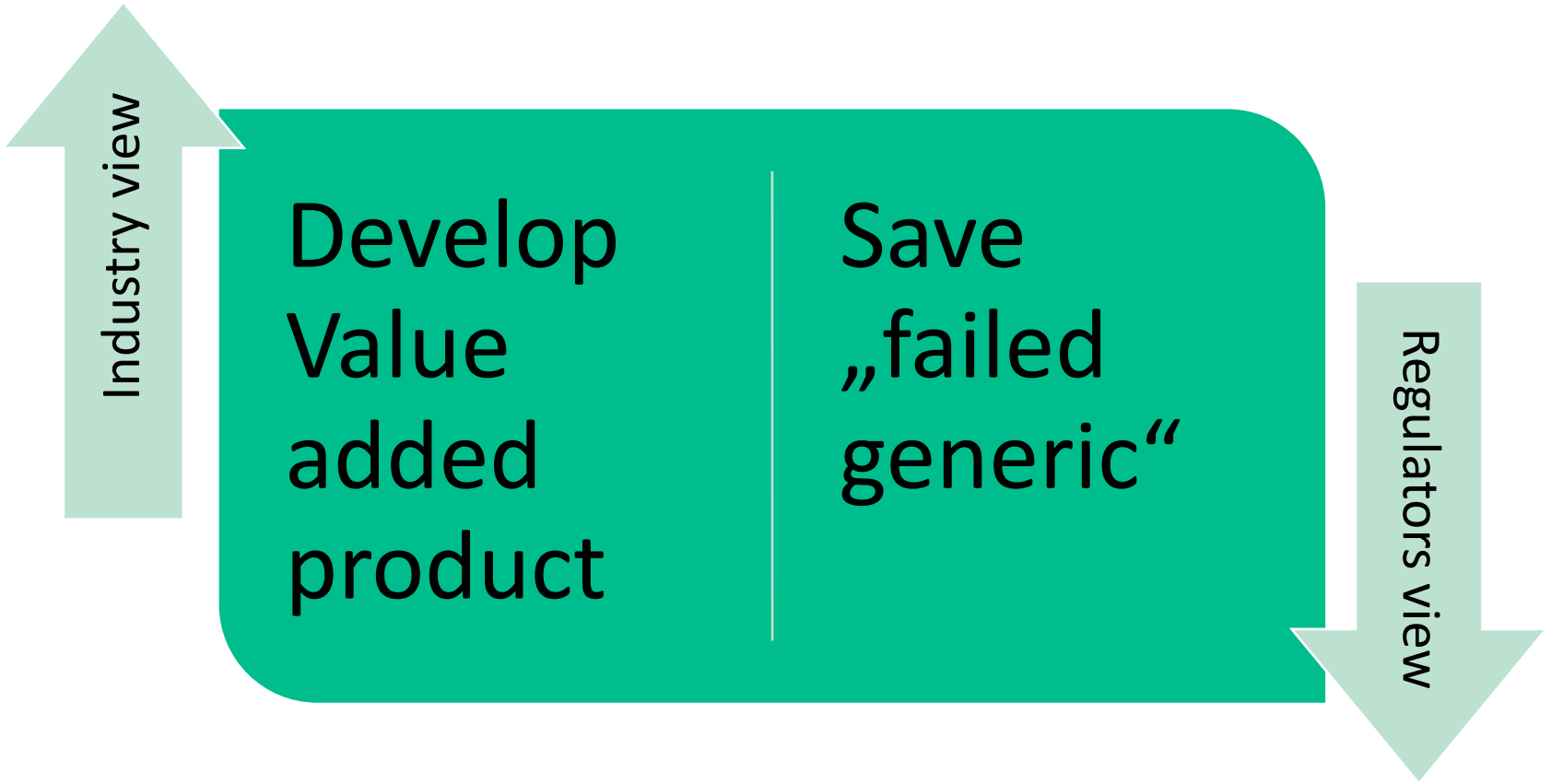
DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND THE COUNCIL
of 6 November 2001
on the Community code relating to medicinal products for human use

Article 10

2. For the purposes of this Article: **(b) 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances** and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Article 10(1) not feasible.

WHAT IST THE HYBRID APPLICATION USED FOR?



QUESTION 1: EXTENT OF CLINICAL DEVELOPMENT

Clinical Pharmacology and Pharmacokinetics: Question & Answers [Section 1.2]:

If suprabioavailability is found, the development of a lower dosage strength should be considered. In this case, the biopharmaceutical development should be reported and a final comparative bioavailability study comparing the reformulated new product with the approved reference medicinal product should be submitted.

Bioavailability studies: pivotal fasting, food effect, dose-proportionality and PPI-interaction are adequate.

Notice to Applicants (Volume 2A, Chapter 1, 2019). The extent of the additional studies required in the framework of an article 10(3) application depends on the changes introduced vis-à-vis the reference medicinal product (...) and will be a matter of scientific assessment by the relevant competent authority.

Annex II: additional data usually required	
d) suprabioavailable products i) same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time	**Bioavailability studies may suffice** (see Bioequivalence guideline)

WHICH GUIDELINES TO FOLLOW, WHEN DEVELOPING A VAM?

in our case guidelines were there (suprabioavailable products)

newer applied before for that purpose?

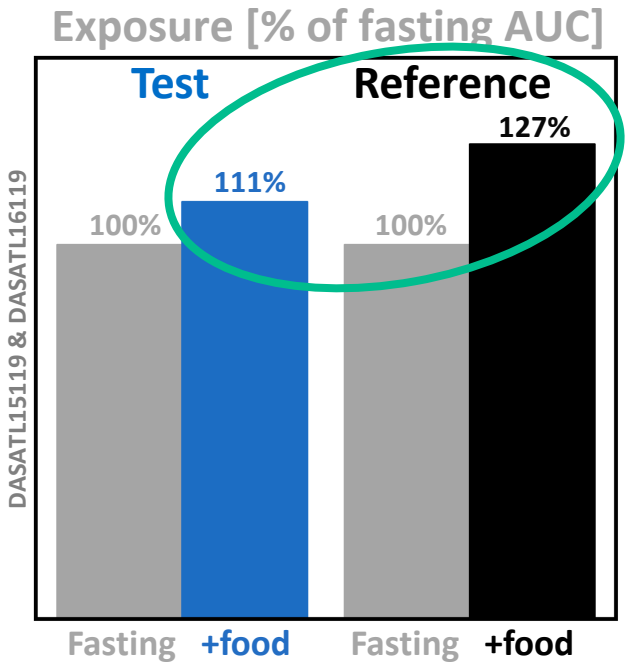
Fenofibrate, deferasirox, buprenorfin/naloxon

QUESTION 2: FOOD EFFECT STUDY

Clinical Pharmacology and Pharmacokinetics: Question & Answers [Section 1.2]:

The potential for a difference in food effect on the rate and/or extent of absorption or a difference in absorption interactions between the reformulated new product and the approved reference product should be discussed and when relevant evaluated in vivo.

Sprycel SmPC [Section 4.2]: The observed food effects do not represent clinically relevant changes in exposure. [Section 5.2]: Sprycel can be taken with or without a meal…



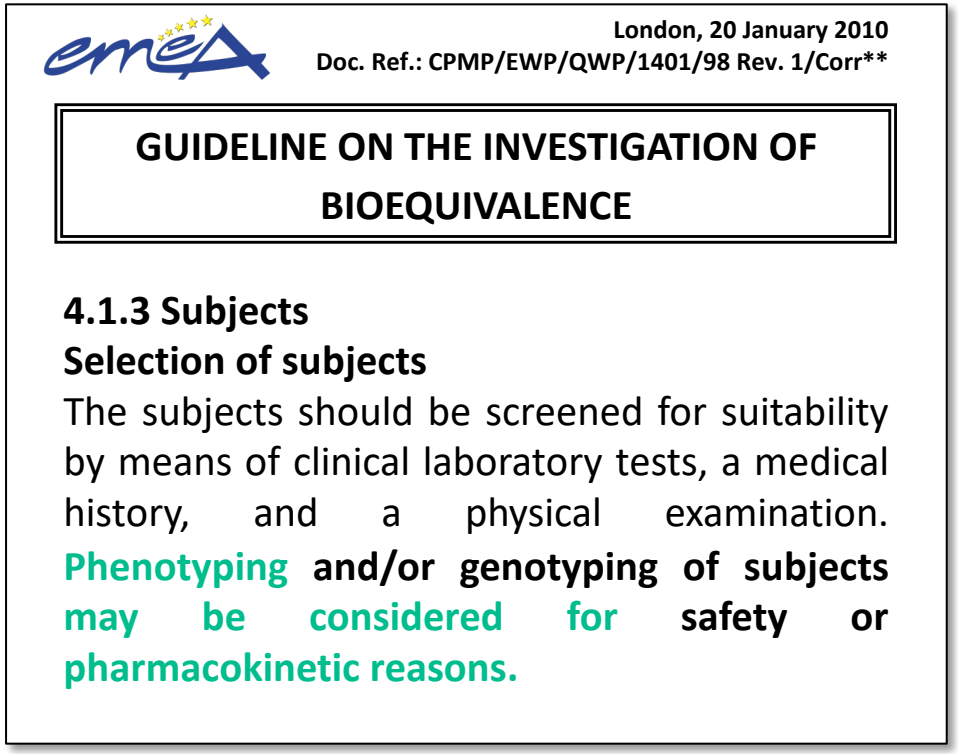
Safe & Efficacious

Exposure of test under fed conditions is within the exposure of reference in fasting & fed state.

QUESTION 2: FASTING STUDY

(1) Dasatinib requires stomach acid for absorption [Yago et al., 2014].

(2) Prospectively applied strategy to avoid random effect of low-liers: standardization is essential for unbiased comparison between Zentiva product and reference.



London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr**

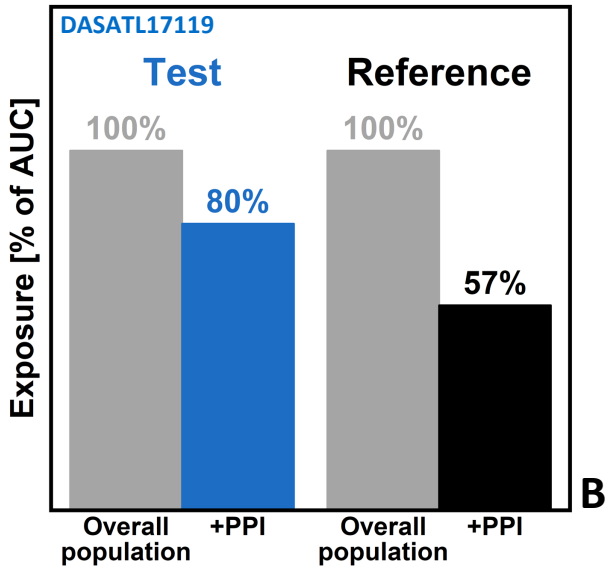
GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

4.1.3 Subjects

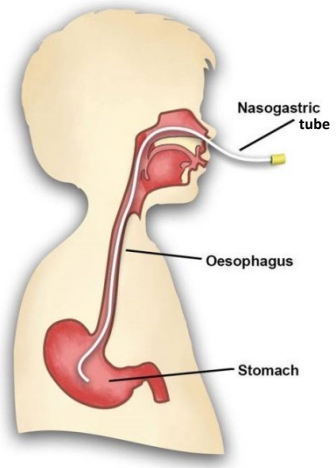
Selection of subjects

The subjects should be screened for suitability by means of clinical laboratory tests, a medical history, and a physical examination. **Phenotyping and/or genotyping of subjects may be considered for safety or pharmacokinetic reasons.**

QUESTION 2: EXTRAPOLATION OF RESULTS



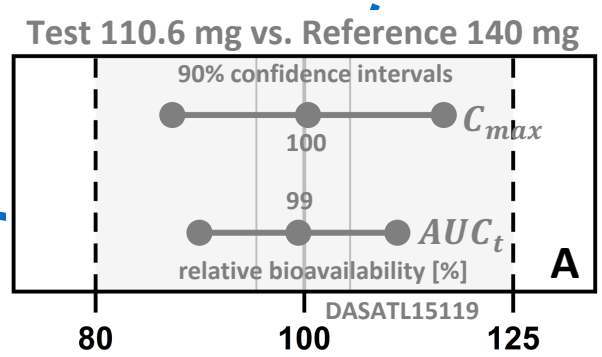
Test product at increased gastric pH: exposure will be higher than reference & will not exceed concentrations in normochlorhydric subjects.



Screening

pH<4

Exposure at increased pH?



Normochlorhydric population

Anafezyn/Daruph

Summary of product characteristics

4.2. Posology and method of administration

Achlorhydria/hypochlorhydria

Dasatinib plasma concentration may be reduced in patients with decreased gastric acidity (see section 4.5). Dose adjustments may be necessary in such situations.

EVOLUTION OF of DASATINIB PRODUCT SPECIFIC GUIDANCE

2015	• Gx companies struggling to prove bioequivalence in a standard fasting study as defined in the first version of product specific guidance
2019	• Our pivotal BE study on preselected population (normochlorhydric) conducted
2021	• Revision 1 of the product specific guidance allowing outliers (less than 10% of AUC) released
2022	• Our approach recognized as viable alternative by PK Working Party during the CHMP referral

QUESTION 3: PPI ADMINISTRATION

Medicare (US): 21.6% patients receiving TKIs for treatment of CML used also PPIs within the first 90 days of TKI therapy [Sharma et al., 2019]

Co-prescription data[1)]			
Dasatinib	2017	2018	2019
Alone	2‘595	2‘868	3‘258
+PPI	623	612	669
%	24%	21%	21%

1) number of patients; sourced from Germany

Concomitant use of dasatinib and PPIs is happening in clinical practice.

Reduction of exposure with PPI administration[1)]		
Product	Full PPI effect[1)]	Staggered[2)]
Test	-46%	-20%
Reference	-86%	-43%

Reduction minimized

1) DASATL09294; 2) DASATL17119

Sprycel SmPC [4.4 & 4.5]: H2 antagonists and proton pump inhibitors are not recommended. … use of dexamethasone, … is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful.

Reduction of exposure for test product allows SmPC claim for staggered administration of dasatinib and PPI/H2RA. Warning in SmPC: 4.4 & 4.5.

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WHAT DRIVES PHYSICIAN´S TREATMENT CHOICES?

ESMO treatment guideline:

Management of resistant and refractory disease

Before defining a patient as having TKI resistance and modifying therapy, treatment compliance and drug–drug interactions should be assessed.

Evidence and consensus based guidelines in medical journals:

• TKIs, various (acalabrutinib, bosutinib, ceritinib, dacomitinib, dasatinib, erlotinib, gefitinib, lapatinib, neratinib, pazopanib)	• Antacids	• ↓ absorption of TKI	• Separate the dose: TKI at least 2 hours before or 4 hours after the antacid
	• PPIs • H2-receptor antagonists	• ↓ availability of TKI	• Consider temporarily stop of the PPI or H2-recept antagonist, or separate the dose: TKI, 2 hours before PPI or H2-receptor antagonist; if this is not possible, TKI directly followed by PPI or H2-recept antagonist, or TKI concomitantly with Coca-Cola

ZENTIVA

Hochhaus: Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2017
Leeuwen: Evidence- and consensus-based guidelines for drug-drug interactions with anticancer drugs; A practical and universal tool for management, Seminars in Oncology, 2022

WHO SHOULD ASESS THE PROPOSED CLINICAL ADDED VALUE?

regulator*	physician	HTA/insurance company	pacient
• standardisation • risk/benefit • conservatism	• real world context • patient outcomes • more treatment options	• reference pricing • hard outcomes • economically driven decisions	• quality of life matters a lot and often determines adherence to treatment

*in our case the PK experts were involved

QUESTION 4: MEDICATION ERRORS

Anafezyn/Daruph

Summary of product characteristics

4.2. Posology and method of administration
[Product] has higher bioavailability than other dasatinib-containing products and **cannot be used interchangeably with other dasatinib formulations** (see section 4.4). **The dose of [Product] have been reduced by 21% compared to other dasatinib products to achieve similar exposure.** In case of switch between dasatinib-containing products, the dosing recommendations of the intended product must be followed.

Risk minimization measures:

(1) **Reduction of dose by 21%: distinct dose strengths as compared to reference.**

(2) **Differences highlighted in the SmPC [Section 4.2 & 4.4] and PIL: warning.**

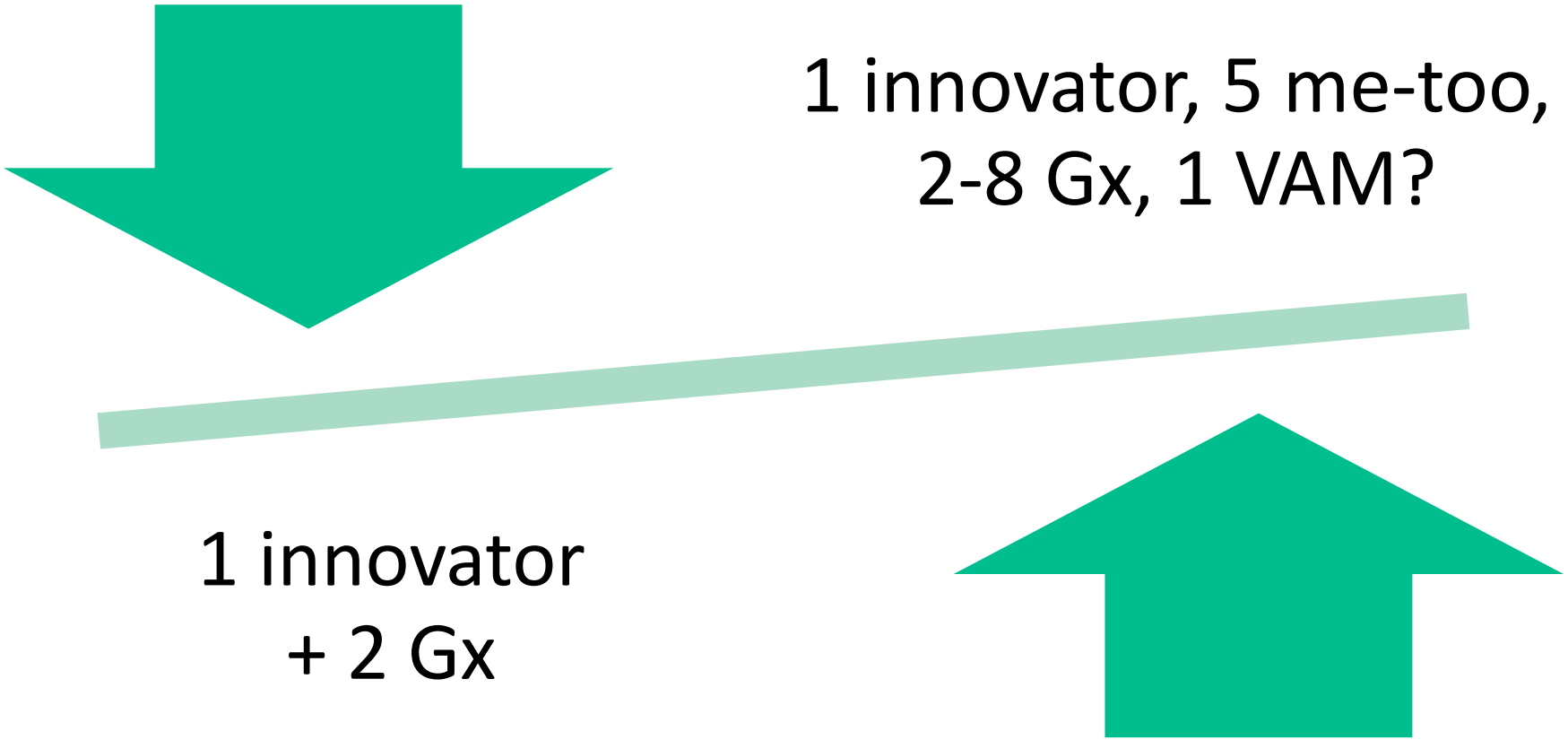
(3) **Warning on outer packaging.**

(4) **Educational materials for prescribers and pharmacists.**

Potential risk for medication errors is adequately addressed by the proposed routine and additional risk minimization measures.

Prescribers have experience in monitoring the effect and adverse effects before taking the decision for treatment continuation, dose escalation, or dose interruption, reductions or discontinuation in case of toxicity.

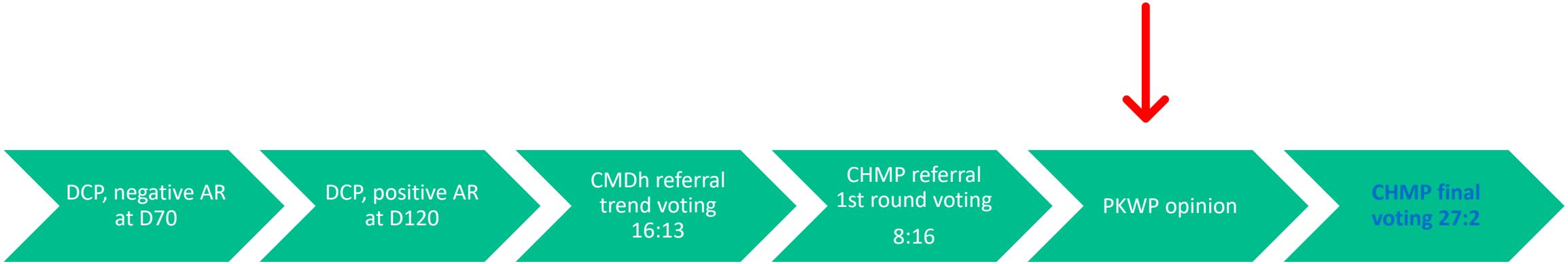
MESS/BENEFIT RATIO



HOW WAS THE BEST CALCIUM CHANNEL BLOCKER FOUND?

- **Amlodipine (Norvasc)**
- Aranidipine (Sapresta)
- Azelnidipine (Calblock)
- Barnidipine (HypoCa)
- Benidipine (Coniel)
- Cilnidipine (Atelec, Cinalong, Siscard)
- Clevidipine (Cleviprex)
- Efonidipine (Landel)
- Felodipine (Plendil)
- Isradipine (DynaCirc, Prescal)
- Lacidipine (Motens, Lacipil)
- Lercanidipine (Zanidip)
- Manidipine (Calslot, Madipine)
- Nicardipine (Cardene, Carden SR)
- **Nifedipine (Procardia, Adalat)**
- Nilvadipine (Nivadil)
- Nimodipine (Nimotop)
- Nisoldipine (Baymycard, Sular, Syscor)
- Nitrendipine (Cardif, Nitrepin, Baylotensin)
- Pranidipine (Acalas)
- Phenylalkylamine
- Fendiline
- Gallopamil
- Verapamil (Calan, Isoptin)
- Diltiazem (Cardizem) also in SR form

TIMING, VOTING AND OUTCOME



RECIPE for a GOOD VAMCAKE

ingredients:

- meaningful idea
- robust technical solution
- well thought trough development plan
- enthusiastic management
- resilient team ready to deal with surprises
- clever consultants
- open-minded RMS

instructions:

steer well all ingredients and bake in preheated oven for 5 years☺

acknowledgment

Jiri Hofmann/Zentiva

Zentiva´s development and regulatory team

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Zentiva´s management