Federal Institute
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The Liver Forum:
Regulatory update from Europe

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No conflict of interest

The views expressed in this presentation are primarily those of the author and do not necessarily express those of the BfArM, nor of the EMA

Regulatory update from Europe: Combination treatment

- **Content:**
- Combination treatment in NASH
  - Theoretical background (EMA FD combination treatment guideline)
  - What can we learn from other fields of combination treatment:
    - » Hypertension (guideline + examples)
    - » Type 2 diabetes (draft guideline + examples)
  - Conclusions for NASH developments

23 March 2017
EMA/CHMP/158268/2017
Committee for Human Medicinal Products (CHMP)

Guideline on clinical development of fixed combination medicinal products

- Basic Scientific Requirements:
  - Justification of the pharmacological and medical rationale
    - » Simplification of therapy alone not sufficient
  - Evidence needs the demonstration of:
    - » Contribution of all active sbustances to the therapeutic effect
    - » Positive benefit-risk of the combination
  - Evidence (which is often based on combined administration of separate active substances) presented is to be demonstrated to be relevant to the FDC

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Guideline on clinical development of fixed combination medicinal products

- Establishing the contribution of each of the substances should include:
  - Identificiation of the population in need
  - Demonstration of the contribution of each substance
- Therapeutic scenarios for FDCs include the following:
  - Add-on treatment of patients insufficiently responding to an existing therapy
  - Substitution therapy of „free combinations“
  - Initial combination therapy
  - FDCs with (a) new active substance(s)

Relates to FDCs only and will not be considered further

Guideline on clinical development of fixed combination medicinal products

- Scenario 1: - Insufficiently treated patients („add-on indication“)
  - PK: Address interaction (with each other, but also with other concomitant medication), incl special populations etc.
  - PD: Understanding of PD is essential. If different dose-levels of one (or more) of the combination partners are established, factorial design studies are recommended
  - Demonstrate superiority in insufficient responders to one or more active substance(s)
  - Pre-condition is the identification of „insufficient response“
  - Usual requirement would be that treatment with each of the single substances is compared with the combination

Guideline on clinical development of fixed combination medicinal products

- Scenario 3: - Initial combination treatment:
  - Definition of patient population requires special attention: Should be in accordance with the requirements of the specific therapeutic area
  - Justification needed that the potential disadvantages are outweighed (Example given: HIV-therapy)
  - The scenario for superior efficacy comprises the following cases:
    - » Two or more active substances have already an established efficacy in the target population
    - » PK enhancer (of one or more active substances with established efficacy)
    - » One or more of the active substance(s) has no individual efficacy in the target population (but e.g. mechanistic data suggest improved efficacy in combination)
      - Demonstration of the rationale and dose-finding may be shortened, but clinical demonstration of the superiority of the combination would still be required.

Guideline on clinical development of fixed combination medicinal products

- Scenario 4: - FDCs with a new active substance(s):
  - Full PK and PD development as for a single substance is expected
  - Full demonstration of clinical efficacy (and safety) as monotherapy is usually also expected (exception given: PK enhancers).
  - The development of combination treatment in a situation with no accepted standard of care will require the full development for each of the substances as mono-therapy

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- What can be learned from other therapeutic areas in which combination therapy is an established principle?
  - » Not primarily related to the development of FDCs
  - » Combination treatment is an established „pathway“ of developments

– Hypertension

23 June 2016
EMA/CHMP/29947/2013/Rev. 4
(Previous ref. number EMA/238/1995/Rev. 3)
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of hypertension

– Diabetes:

(Draft guideline)

14 May 2012
CPMP/EWP/1080/00 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

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- Learning from other therapeutic areas:

  <u>Diabetes (type 2):</u>

  – General requirements for demonstration of efficacy for new substances:
    - » Demonstrate superiority over placebo in at least 1 mono-therapy study
    - » Demonstrate superiority over placebo when added to an established background therapy
    - » Demonstrate non-inferiority to an active comparator (mono-therapy or add-on)

  – Mono-therapy studies: Compulsory requirement;
    - » use „early stage“ patients;
    - » duration not more than 6 months;
    - » adequate rescue therapy should be provided

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- Learning from other therapeutic areas:

  Diabetes (type 2):

  – Add-on therapy (=combination treatment):

    » For patients „insufficiently treated“

      - Either with „insufficient background medication“ or
      - Switch to different active (e.g. for 12 weeks) and testing combination after demonstration of insufficient response (=choice of similar background for all patients)
      - Assure stable dose of background
      - Avoid dose adaptation

    » Rational of choice of combination should be provided and be based on recommendations from learned societies

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- Learning from other therapeutic areas:

  Diabetes (type 2):

  – Newer examples for licensed combination products:

    » Standard license:

      - [the combination] is indicated
      - to improve glycaemic control when metformin (and/or sulphonylurea (SU)) and one of the monocomponents of [the combination] do not provide adequate glycaemic control,
      - when already being treated with the free combination of (the two components).

    » „Initial second line combination“

      - [the combination] is indicated
      - to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control

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- Learning from other therapeutic areas:

  <u>Diabetes (type 2):</u>

  – Newer example for an „initial“ combination under development:
    - Regulatory assessment to be awaited!

  – VERIFY study:
    - A 5-year Study to Compare the Durability of Glycemic Control of a Combination Regimen With Vildagliptin & Metformin Versus Standard-of-care Monotherapy With Metformin, Initiated in Treatment-naïve Patients With Type 2 Diabetes Mellitus
    - Expected date for completion: April 2019
    - Patient population:
      - Treatment naïve population with newly diagnosed T2DM (within 24 mo.)
      - HbA1c between 6.5% and 7.5%
    - Primary Endpoints:
      - Rate of loss in glycemic control over time [Time Frame: Week 26]
      - Time to initial treatment failure [Time Frame: 5 years]

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- Learning from other therapeutic areas:

  Diabetes (type 2):

- Summary:
  - Combination treatment development in diabetes is well-established and requires:
    - » Demonstration of efficacy also in the mono-therapy setting
    - » Combination therapy is expected to be tested against a known (well established) background medication
    - » Combination therapy requires the demonstration of an „insufficient response“ (either to mixed background, or to a dedicated standard agent)
  - There is no recommended pathway for the development of „initial combination treatment“, and/or the development of more than one new active substance at a time.
  - Combination therapy programmes are facilitated by the availability of a universally accepted biomarker to be used as primary endpoint (=HbA1c)

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- Learning from other therapeutic areas:

Hypertension:

- General principles for study design for new substances:
  - » Actively controlled studies are considered gold standard (comparing with „reference therapy“, showing at least a „similar benefit/risk of the drug“)
  - » Placebo-controlled mono-therapy studies can be added at the end of a study in the form of a (randomised) „withdrawal phase“.
  - » At least one combination study with at least one other standard antihypertensive agent is mandatory
  - » General study duration recommended to be 3-6 months (at least 6 months for actively controlled studies)

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- Learning from other therapeutic areas:

  Hypertension:

- General principles for patient selection:
  - » Patients with mild to moderate BP increases are suitable for studies in which (current) therapy is withdrawn in order to investigate the effects of mono-therapy
  - » Patients with markedly elevated BP are thought to require a continuous uncerlying antihypertensive therapy and thus not suitable for mono-therapy investigations (=compulsory „combination treatment population“)
- General principles for the primary endpoint:
  - » Arterial blood pressure is the undisputed primary endpoint in trials on hypertension
  - » “BP lowering effects of anti-hypertensive therapy should be documented as the pre-/post-treatment reduction of BP. SBP is the preferred efficacy variable whilst DBP is a mandatory secondary end point.”

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- Learning from other therapeutic areas:

  Hypertension:

- Fixed dose combinations:
  - Combination therapy is commonly applied in the therapeutic area
  - Combination is usually recommended if:
    - » The combination treatment is biologically plausible
    - » FDCs are expected to have proven effiacy and safety for the mono-substances, as well as for free combinations
    - » Demonstration of the contribution of each of the substances is expected.
  - Scenarios given:
    - » Initial combination treatment – see next page
    - » Second and third line treatment
      - Suitable when response to one or more mono-components is insufficient
    - » Substitution therapy
      - For patients adequately controlled with free combination

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- Learning from other therapeutic areas:

  Hypertension:

- „Initial combination treatment“ or „first-line FDCs“ main requirements:
  - Initial combination treatment“ (first line FDC treatment) is usually preserved for patients with:
    - » A low chance of being sufficiently treated with one agent (e.g. level of hypertension; demographic factors etc.)
    - » The patient population has a high risk for CV events
- Key elements:
  - Demonstration of safety
  - Objective: Blood pressure control is achieved in more timely manner than with standard treatment (initial mono- followed by combination treatment)
  - Compare different doses of initial combination with one or more „late escalation“ arms.
  - Key efficacy parameter is „Time to achieve target BP“

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- Learning from other therapeutic areas:

  Hypertension:

- Example of a newer (and only!) license for an „initial“ combination therapy product:
- Viacoram (Perindopril/Amlodipine) (decentralised license; not via EMA!)
  - FDC of Perindopril/Amlodipine first approved 2008 (strengths: 5/5; 5/10; 10/5; 10/10) with a „substitution indication“
  - Viacoram as first-line with the strength of 3.5/2.5
    - Indication granted: „Treatment of arterial hypertension“
    - Contrary to the „usual“ FDC-indication: XXX/YYY is indicated in adults whose blood pressure is not adequately controlled on XXX or YYY monotherapy.
  - As second line-therapy with the strengths 7/5; 14/10.
  - First-line indication mainly granted on the basis of improved safety in comparison to the full doses of the mono-components!

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- Learning from other therapeutic areas:

  Hypertension:

- Summary:
  - Combination treatment development in hypertension is well-established and even considered an integral part of the development programme
  - Combination treatment is usually restricted to the patient population not adequately responding to mono-therapy and/or standard treatment
  - „Initial combination“ treatment (even including more than one new substance) is a possible way forward but requires the identification of a special patient population, as well as the use of a special endpoint
  - There is an established classification of the severity of the disease, which can be used to identify a population suitable for combination treatment
  - Combination therapy programmes are facilitated by the availability of a universally accepted biomarker to be used as primary endpoint (SBP)

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- Overall Summary:
- Lessons learnt from the FDC guideline for NASH combination therapy developments:
  - The development of FDCs (and in general of combination treatment) requires a clear rationale, based on PD, separate dose-finding, as well as demonstration of clinical advantages (comparative safety and efficacy)
  - The development of „initial“ treatment with FDCs (and combination treatment in general) is difficult in a situation for which no established treatment modalities exist
  - The development of a FDC (and free combination treatment) with one (ore more) new active substance(s) requires the separate, full development for the single substance(s).
  - Theoretically, the development of the FDCs in NASH (or the free combination), could be done at the same time with the single substances, but is hampered for the following reasons:
    - » Combination treatment is not an established principle in the disease area
    - » Missing or unclear definition of „insufficient response“
    - » Missing definition of an appropriate „target population“
    - » Missing of a well-established surrogate endpoint

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- Overall Summary (2)
- Lessons learnt from other indications for NASH combination therapy developments:
  - The separate evaluation of mono-therapy is compulsory in diabetes, whereas only restricted requirements apply for hypertension.
    - » In NASH, there are currently no established principles but all current developments in later clinical stages use mono-therapy only
  - The availability of a universally accepted biomarker is the basis of the requirements in both disease areas.
    - » Such a marker is currently not available in NASH.
  - It is well-established for both diabetes and hypertension that „insufficient response“ patients are candidates for combination treatment.
    - » Such criteria have not been established in NASH, but might be developped on the basis of the currently discussed histology response criteria (e.g.: any deterioration of NAS score and no change in fibrosis stage).

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- Overall Summary (3):
- Lessons learnt from other indications for NASH combination therapy developments:
  - The development of combination treatments in hypertension also includes the possibility to investigate „initial combination“ but requires the identification of patient population with high medical need.
    - » Can such a population be identified in NASH? (e.g. could it be a fibrosis stage III/IV population with high NAS activity?)
  - In arterial hypertension, the design of „initial combination“ treament trials uses an endpoint different from the established endpoint
    - » Can such a requirement be transferred to the clinical situation of NASH patients? (If it is the above population, the endpoint could be decompensation events?)
  - It should be kept in mind that all these considerations refer to efficacy only. The demonstration of an acceptable level of safety, however, remains a potential issue!

Thank you for your attention!

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