EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Parallel Scientific Advice By EMA with MAHs & HTAs

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Chair, CHMP

Scientific Advice

Advising Applicants on the scientific requirements for marketing authorisation :

- **Before** the first marketing authorisation (MA): companies ask questions on manufacturing, non-clinical and clinical trials, risk-management plans, ways to develop generics and biosimilars; significant benefit for orphan medicines; development in children.
- **Post-MA**: extension of indication to different age groups and stages of the disease; different conditions & safety aspects.

Scientific Advice Working Party of the Committee for Human Medicinal Products (CHMP)

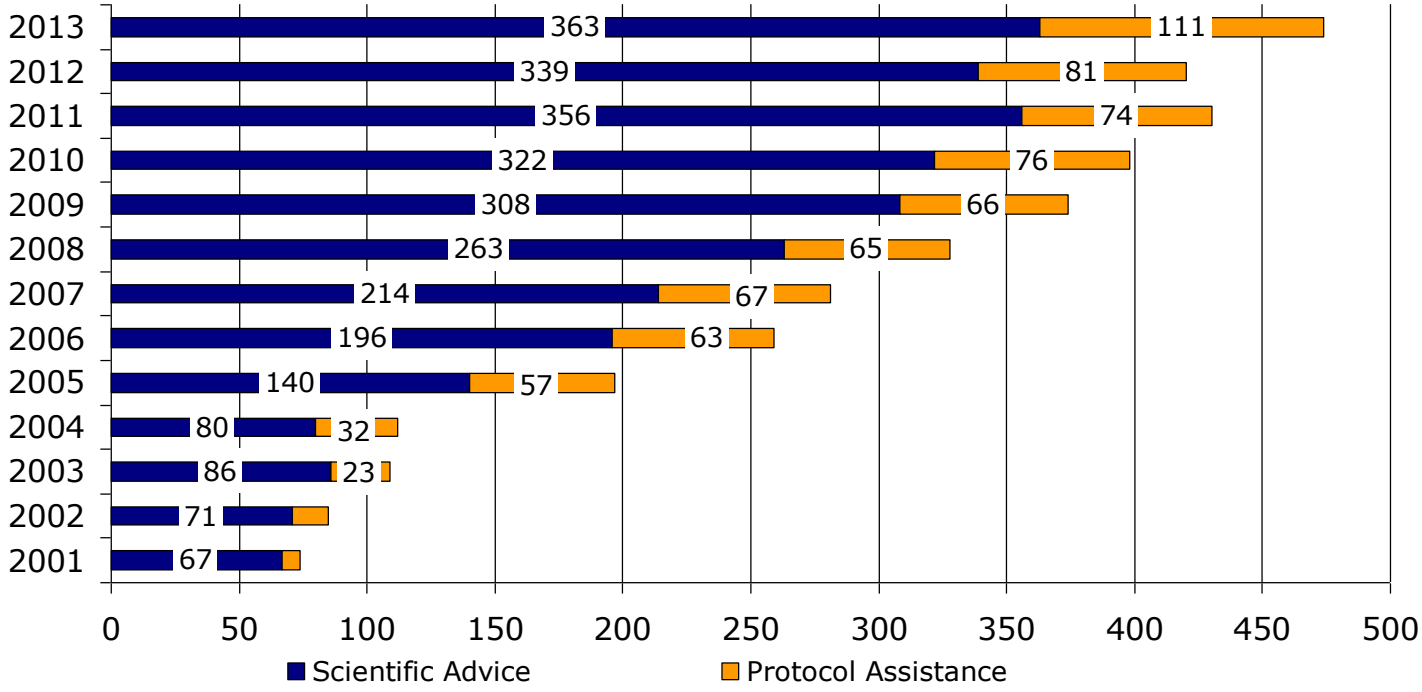
- 30 experts from national authorities, universities and hospitals selected for expertise: e.g. oncology, cardiology, psychiatry, neurology, immunotherapy, gene and cell therapy, pediatrics, geriatrics; quality, non—clinical and statistical methodologies.
- Joint members across Committees not only CHMP, but also Paediatrics, Orphan, Advanced Medicinal Products (**& PRAC**)
- Scientific and logistic support from EMA secretariat: 10 medical doctors /pharmacists and 7 assistants

Scientific Advice Working Party of the Committee for Human Medicinal Products (CHMP)

- 3-4 day meetings per month (except August)
- Networking many thousands of EU experts

Scientific Advice main activity so far:

Scientific Advice and Protocol Assistance for orphan drugs



Qualification of Novel Methodologies

- **Vision**: Speed up/optimise drug development and utilisation, improve public health
- Procedure to guide the development of new more efficient ways to develop drugs, e.g. development of new endpoints for clinical trials:

  E.g. Can changes in chemicals (biochemistry) or structures (imaging/MRI) in the brain predict the development of Alzheimer's disease before the patients lose their memory and cannot function so that a medicine can intervene early on and be more effective?

- Started 2008: 60 procedures so far

Qualification of Novel Methodologies for drug development

CHMP Qualification Advice on future protocols and methods for further method development towards qualification.

CHMP Qualification Opinion on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.

Who can apply? Consortia, Networks, Public / Private partnerships, Learned societies, Pharmaceutical industry.

Qualification of Novel Methodologies

Methods to **predict toxicity**

Inclusion criteria to **enrich a patient population** for a clinical trial: Volume of certain brain structures and level of certain biochemicals in the cerebrospinal fluid for trials in Alzheimer's disease

Surrogate endpoints: new sensitive scales to measure efficacy of a new drug instead of hard clinical endpoints

Patient and caregiver reported **outcomes**

Qualification of Novel Methodologies

Preclinical development

- pharmacological screening
- mechanism of action
- **predict activity/safety**
- PK/PD modelling
- toxicogenomics

Clinical development

- verify mechanism
- dose-response
- proof of concept
- **enrich population**
- **surrogate endpoint**
- Early detection of safety signals

Drug utilisation

- optimise target population
- guide treatment regimen

Scientific advice together with Health Technology Assessment bodies (HTAs)

- Possibility for Applicants to discuss together with Regulators and Health Technology Assement bodies (HTAs) early in development what is needed to not only for the benefit/risk asessment (Regulators) but also decide on the added value (HTAs) so that HTAs recommend reimbursement and the product gets to the patients.
- Started 2010: **35 procedures so far**, HTAs from UK, Italy, France, Sweden, Germany, Spain, Netherlands, Belgium
- Workshop on the 26th of November 2013 attracted more than 300 participants: regulators, HTAs, Industry, SMEs, Academia, Health Care Professionals, Patient representatives, European Commission.
- So far - **10 this year (!)**

Parallel HTA-EMA SA-experience so far

- Diabetes, Heart Failure
- Alzheimer's, Depression
- Lung Cancer, Breast Cancer, Melanoma, Pancreas-Ca, Mesothelioma, Leukaemia, Cachexia in cancer
- Asthma, COPD, Rheumatoid Arthritis, Osteoporosis
- Multi-resistant Infections,
- Food Allergies, 2 Gastroenterology conditions
- Orphan conditions; Cell therapy; Ophthalmology

The majority are new mechanisms of action in the respective area, new monoclonal antibodies, new chemicals, tumour vaccines.

Parallel HTA-EMA SA

Experience so far

Common discussions: Elements which are necessary for the benefit/risk assessment (Regulators) and added value (HTAs)

- Comparator: placebo, active comparator
- Clinical endpoints: Survival, quality of life
- Duration of the trial
- Patient population to be included premarketing / post-marketing

Parallel EMA HTA Experience - Advantages

- **Interaction** between HTA and regulators; listening to each others views, improves understanding, and allows contemporaneous evolution of your development to satisfy all parties before development plans and HTA/EMA decisions have been finalised
- To review respective positions and **identify critical divergences**
- **Life cycle approach** – PAES & PASS

EMA/HTA: Ongoing activities

- EMA-HTA group (EMA, GBA, Aifa & NICE) works on procedure to be published for consultation
- Post Authorisation Efficacy Studies (PAES)
- EMA pilots on "Adaptive Licensing" ("AL")
- EMA participates also in the SEED Consortium (Shaping European Early Dialogues), led by the French Haute Autorité de Santé (HAS), who won the EC Call for Tender: 14 HTA bodies, 7 procedures on Medicinal products planned for 2014.
- Can EMA further facilitate dialog between HTAs prior to a specific SA?

Scientific Advice – Challenges

- Reinforce SA throughout the **life-cycle of the product**: currently (only) 25% of the SA procedures are for products which have an initial MA. Integrate better Health Technology Assessment Bodies including parallel SA with HTAs peri- and post-licencing. (PAES, AL)
- **Integrate better also other Stakeholders** like Patient Representatives, Health Care Professionals, Academics , Learned Societies. (AL)
- Integrate better **Modelling&Simulation** (through the newly formed M&S Working Group) throughout the life-cycle of the product

EPARs.....

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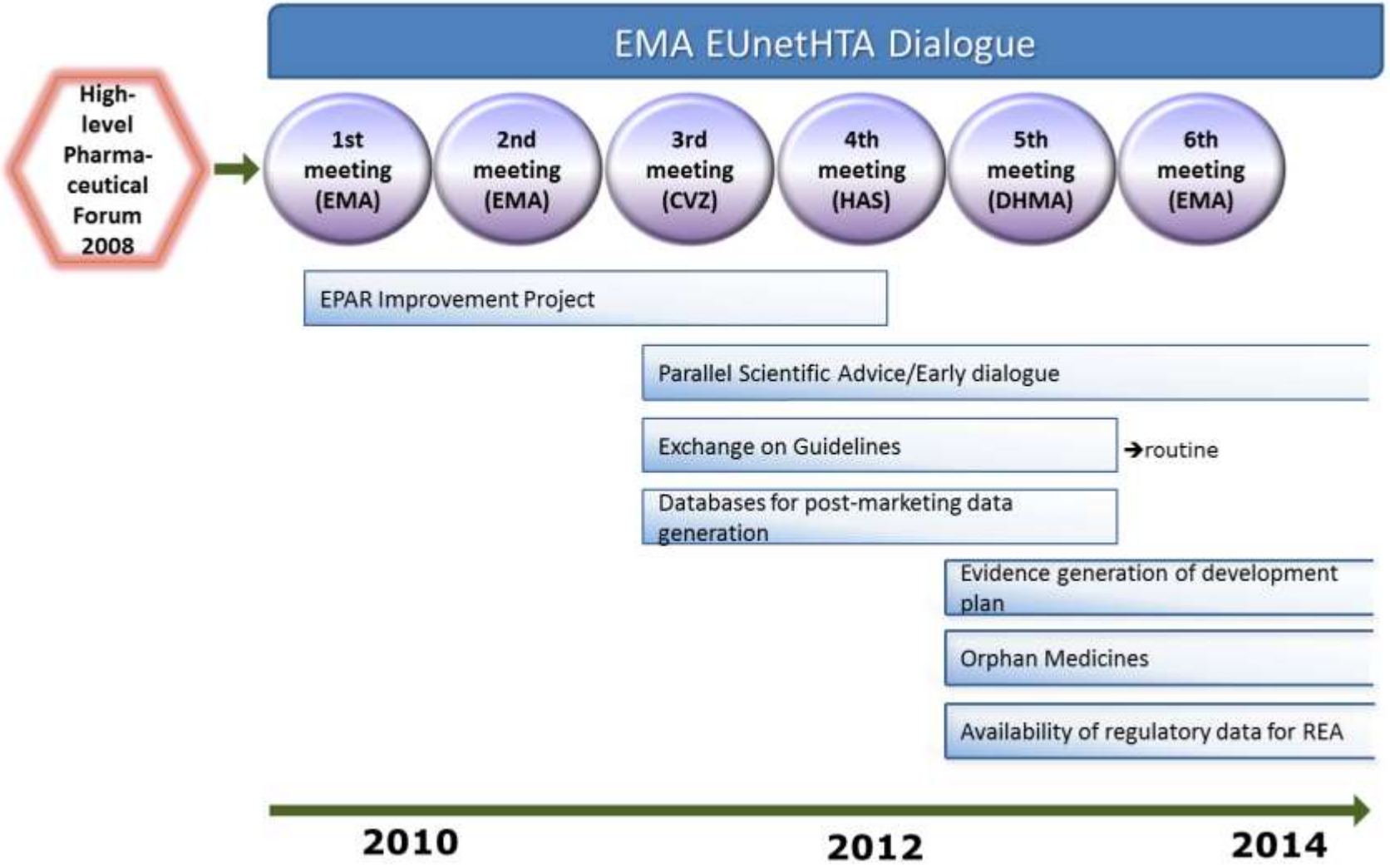
Brücke zwischen Zulassung und Health Technology Assessment (HTA) Bewertung

DGRA Annual Congress, 20 June 2013, Bonn

Presented by: Michael Berntgen
Head of Rheumatology, Respiratory, Gastroenterology and Immunology
Safety & Efficacy of Medicines

An agency of the European Union


EMA EUnetHTA Dialogue
High-level Pharma-ceutical Forum 2008
1st meeting (EMA)
2nd meeting (EMA)
3rd meeting (CVZ)
4th meeting (HAS)
5th meeting (DHMA)
6th meeting (EMA)
EPAR Improvement Project
Parallel Scientific Advice/Early dialogue
Exchange on Guidelines
→routine
Databases for post-marketing data generation
Evidence generation of development plan
Orphan Medicines
Availability of regulatory data for REA
2010
2012
2014

"EPAR improvement" project

Summary of changes in the templates and guidance:

Area	Updated Section (s)	Brief description of changes introduced
General	List of Abbreviations	• A comprehensive list of all abbreviations used throughout the assessment report has been included
	List of References	• Consider generation of a reference list
Quality	Section relative to the Active Substance	• Addition of the structural formula for chemical substances and of structural characteristics for biologicals
Non-clinical / Clinical	Discussion on (non)clinical aspects	• Guidance is given in order to ensure that all information in the SPC is explicitly assessed and supported by the scientific assessment
Clinical	Discussion on clinical efficacy and clinical safety	• Additional guidance is given on how to discuss critical aspects of the design like endpoints and comparators • More explicit reasoning of the CHMP's view on the data and the analysis (including additional analysis) in the context of the final conclusions is encouraged, as well as discussion of the shortcomings of the data
	Summary table on main efficacy studies	• Inclusion of a standardised tabular overview of the main efficacy data from the pivotal studies

EUROPEAN MEDICINES AGENCY
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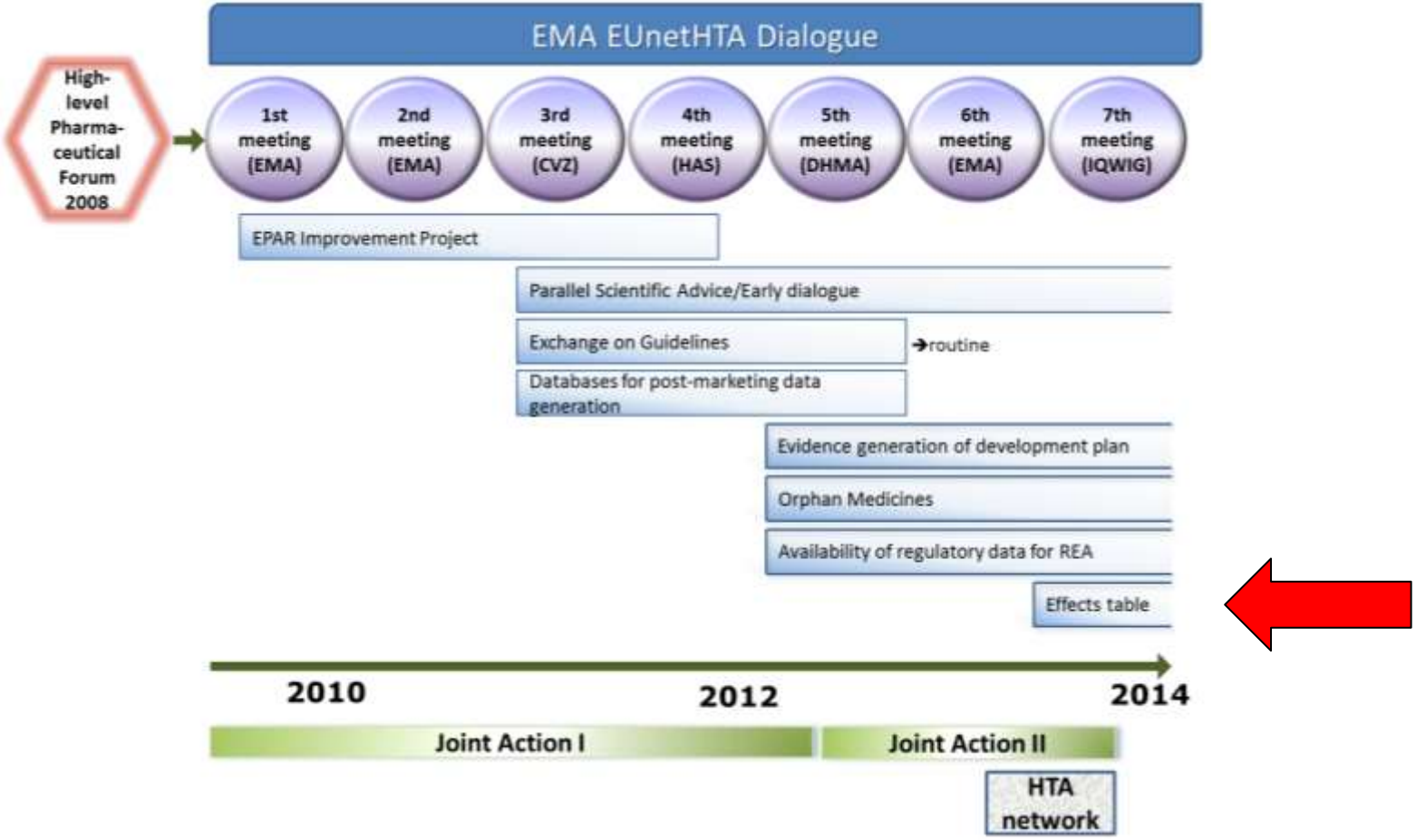
G-BA conference "Drei Jahre frühe Nutzenbewertung" – Contribution from the European Medicines Agency

Berlin, 30th April 2014

Presented by: Michael Berntgen
Head of Scientific & Regulatory Management Department

An agency of the European Union

Collaboration between regulators and HTA bodies on European level



Examples for the variety of opportunities for exchange and collaboration

"Effects tables" used by regulators and HTA bodies for their respective decision making

Methodological aspects of study design., e.g. ENCePP HTA working group regarding pharmacoepidemiological studies or workshop regarding scientific guideline for PAES

Guideline development (methodological and clinical guidelines)

Presentation of data and provision of assessment reports

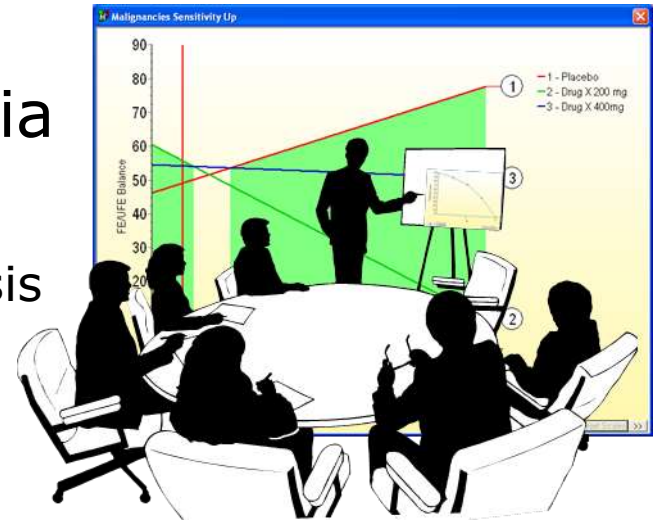
New approaches for data generation, e.g. IMI GetReal

Initiatives and efforts in the interest of serving public health

The proposed toolkit

- Qualitative method: Effects Table
  - Compact display of effects and information for the benefit-risk balance
  - Can be generally applied, can be used as basis for quantitative methods

- Quantitative method: Multi Criteria Decision Analysis (MCDA)
  - Allows higher precision, sensitivity analysis
  - Requires substantial resources to build model



Effects table

Recommended by the B/R Steering Group to:

1. Provide clarity on the presentation of quantitative data used for the assessment of the product to support the B/R assessment
2. Facilitate communication of the B/R assessment across committees and with stakeholders
3. Increase consistency of the quantitative data used in assessments across a drug class

ET example – Caprelsa for thyroid cancer

	Effect	Description	Unit	Placebo	Vandetanib	Uncertainties/ Strength of evidence	References
Favourable	PFS (HR)	From randomization to progression or death (blinded independent review)	N/A	1	0.46 95% CI: (0.31, 0.69)	Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?)	See Discussion on Clinical Efficacy.
	PFS (median)	Weibull model	Months	19.3	30.5	Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy?	Single-arm study in RET negative patients post-approval.
	ORR	Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST	%	13	45	No clear effect on PRO/QoL (missing data)	See Discussion on Clinical Efficacy.
Unfavourable	Diarrhoea Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; Life-threatening	%	2.0	10.8	Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment.	Risk of dehydration and renal/cardiac risks (see SmPC 4.4)
	QTc related events Grade 3-4	QTc >0.50 second; life threatening; Torsade de pointes	%	1.0	13.4	Risk of developing further major cardiac SAEs including Torsades de pointe?	Restrict to symptomatic and aggressive disease (see SmPC 4.1).
	Infections Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening	%	36.4	49.8		Explore lower dose (see See Table 20. Summary of the RMP)

Pilot of the ET

- Phase I pilot completed in May 2013
  - Table prepared by rapporteur and attached to reader's guidance
  - Positive feedback on average

- Phase II pilot agreed at July CHMP (2013)
  - Include initial applications for New Active Substances
  - ET incorporated in the B/R section
  - Rapp. and Co-rapp. to include the ET at D80 AR
  - ET to be kept updated until D210
  - 12 products completed in total

In summary…..

Collaboration between stakeholders is the way forward:

- Scientific Advice/Adaptive Licensing
- Transfer of knowledge (EPARs etc)
- Generating knowledge
- etc

Thank you very much!

Back-up slides

EMA/HTA: Novel Therapy for COPD

- Company proposed a licensed comparator
- EMA agreed with licensed comparator
- HTA want to be able to compare value of new therapy compared to what it will replace, even if comparator is not licensed for use

- Solution: Introduction of new arm to pivotal study to include both options

EMA/HTA: 2nd line treatment for a rare cancer

- No product authorised
- Company proposes placebo as control
- EMA agrees
- One HTA body requests a particular active comparator used in their country albeit not authorised
- 2nd HTA body requests placebo, they cannot accept by law a non authorised comparator

– Solution: Comparator Investigator's best choice

Parallel EMA/HTA SA

Questions for the HTAs only: Modelling of disease

- The economic evaluation for a drug that slows or delays the progression of Alzheimer disease (AD) relies on the evaluation of the costs attributable to AD had it progressed to more severe stages. As the Phase 3 clinical program may not be long enough to capture the course of the disease, do the HTAs agree that other clinical trial data may be used to model the natural course of AD across time?

Parallel EMA/HTA SA

Questions for the HTAs only: Impact on the caregiver

- Do the Stakeholders consider the impact to the caregiver (e.g. time assisting or supervising patient) an important piece of the value proposition when evaluating a treatment for prodromal Alzheimer's disease?

- Do the Stakeholders agree with the selection of instruments in the clinical trial to capture the burden to the caregiver (Dependence Scale)? Are there any other data that should be collected?

- Overall cost-effectiveness of the product:
  - delaying progression may also extend life expectancy
  - Modelling is necessary to project out the implications of potential post-trial scenarios

Parallel EMA/HTA SA

Questions for the HTAs only: Early use of new antibiotics

- Company argues that appropriate use of new, higher cost antibiotics as initial empiric therapy delivers greater overall benefits to health systems than holding them in reserve. Whilst doing so may result in short term increases of drug acquisition costs, this approach will minimise longer-term societal costs due to a reduction in the emergence of resistance, and the potential to prolong the utility of all antibiotics. What is the view of the participant HTAs?