

#### European regulatory views on benefit-risk assessment methodologies

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### Content

- A short introduction to Benefit/Risk assessment at the EMA
  - The new CHMP Benefit-Risk AR template
  - Effects Table
- Potential use of quantitative B/R methods in drug evaluation





# Marketing Authorisation for Taxotere (docetaxel, 1995)

The Committee for Medicinal Products for Human Use (CHMP) Members have, during the review process, agreed that the application contains sufficient clinical data to support clinical safety and efficacy allowing a positive recommendation for granting marketing authorisation.



### Marketing Authorisation for Ninlaro (ixazomib, 2016)

#### Benefit-risk-balance¶

· Benefite 7

#### \*Seneficial-effects?

In pivelal bial, die waarmibbigkt regimen hade 35 teimprevenentien die gemaar of gescherzy-ondgesch?? eengaard de glaas beregimen and reached a statistically word eant difference (Hidlen APS 20.6-mendie Insasemib va 14.7-mendie glaasbey HR=0.742, d574 CI (0.557, 0.559, g=0012).7

Programion-free Survival-analysis in all subgroups appulations was in favour of transmits regiment (RRC1), including subgroups with obtained program to a sub-factors and a regar, with the exception of patients with section constraints clearness < d(m)(m(n,RR-1,122),122),122)

Overall-Survival favours the instamb regimes (motion OS not reached in either arm; HR+0.000; 45%-Cr: 0.615.4.316).5

The instant brogimen delay of the time to data to progression by approximately 4-months (median-TTP-11.4-months in the instantibum va-15.7-months in the glass boarm; HR=0.712; CI 0.556,0.912;-

Reasonad to the almont was reported with statistically stand cantid fference information Capital - Holding events (capital - CAPPS (OR - 1.44 (.1.03, 1.03), --0.035), CR+VGPR (OR - 1.45 (1.05, 1.95), -0.014) and CR (OR - 1.87 (1.10, 3.16), -0.019) (1

Duration of cappenes to treatment in larger with inseemable optimen with modium COX-20.5 members reasonib (16.62,441) vs.13.0 m aloos be (11.92,441),5

Additionally, the supportive data from the China Continuation Study-provided a statustical and di significant officies in forms of PFS (NR=0.298), P=0.028), A

#### \* Occurtainty-in-the-knowledge-about-the-baneficial-effects\*

gdated officera y data from a second interm analysis representing the most oprio date data, she educed difference in effect between arms in the overall diff organization for Provingence rates a time to programme compared to previous analysis. The hazard ratio (05% C1) for the updated P75-analysis was 0.515 (0.57,1.0) compared to 0.742 (0.557,0.539) as an error previously -1 Although Aigher official work observed in the subgroup of patients with a Licent 2 prior through a, this observation is not supported by supropriets adjustments for multiplicity and lacks convincing belogial and clinical plauability. (

Seased on the observe, and daking into account this this is an application based on a single priorial study , force is asome uncertainty about the magnitude of the treatment offect. The further support the random behaved in the priorial priori, the applicant initiation (the disc) affect of the following studies: study. Control China Cardination - phase 3, randomized, deable blind, multicenter study company and instantib phasicanide and desarrollaters - ensugilate begins instantion and desarrollaters instantib phasicanide and desarrollaters - ensugilate begins instantion and desarrollaters instantibility and the study of the stu in a curra events with relation and environments also include the antice of the meters, cause of a start of the series with a second second the series with a second second the second terms of a start of the second second second terms are set as the second s

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The combination of Studies C16014 and C16019 covers the entre spectrum of extents with newly

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The overall data to be accumulated in various subgroups of multiple myslems patients is a sufficient to provide comprehensive ovdence of officacy, including in patients who have re-lease one grain the apy of

above studies are enging and therefore donotinate concernsion their feasibility. Oats is ented to be anywided by the applicant for the Chine Continuation study by December 2018. for the study C16014 by Occomber 2017, for the study-C16019 by Occomber 2018 and for study 46444 5001 by Occomber 2019 (see Annex 1), 1

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In addition, the Applicant will automit the results from IGNM-5001 study, a clobal, presentive, noninterventional, discrivational study of presentation, dreatment patterns, and outcomes in HM patients, which will also contribute to comprenetive officery data. 1

The spread of the difference of the spread of the difference of the difference of the difference of the spread of the difference of the d nposof-as a gost-sul·lisriaston officery atudy in accordance with Arbido1(2)(a) of Commission clogated Regulation (5U) No.357/2014 (acc Annox 114o the CMMP Opinion).¶

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There are no important uncertainties in the knowledge of unfavourable offsets (

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'7. Recommendations-following-re-examination¶

Sascé on the CHMP review of data on quality , safety and officary, the CHMP review include initial agricole and in-ta-final agricole concluded by majority designs that the bare fit risk balance of Ninkroin-the fullowing includes of

"In NARC in combination with level domitio and downs there as indicated for the creatment of adult patients with multiple myslome who level or creatived at least one prior thereby "1

vas favourable and that the application satisfied the order a for authorization and recommended the granting of the conditional marksting authorization 5

Divergent-positions to the majority recommendation are appended to this report \$ The CHMP disreferer ecommends the granting of the conditional marketing authorized on subject to the following an of times 7

Conditional or restrictions regarding supply and use

Medicinal product subject to react interference processor (see Anna N1: Summary of Product Characteristics, section 4: 2), 5 Conditional and requirements of the Marketing-Aut

---- Periodic-Sefety-Update-Reports-1

The requirements for submission of periodic safety update reports for this medicinal product are solved on the dust are solved by t The marketing-outhersation-holder shall submit the first-periodic safety-update report for this product within 6-months following-outhersation, 1

Conditions or restrictions with reserve to the selfs and offestive use of the medicinal aredust Other-conditions or restrictions reparding supply and use 1

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The MAH shall perform the required pharmace vertances at vitice and interventions datailed in the agreed AMP presented in Hodule 1, 2, 2 of the Harketing Authorisation and any agreed autoaquest. An undeted 202 also did to a desired 1

able-52.-Effecte-7 the treatment of patients with enabling any shows we are available repy-(dete-cut-off:30-October-2014 (14-1A) and 12-30/y-2015- (2\*4-6A)¶

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•	HR-0.742-(	0.587,-0.9	59)¶			(CHMP-AR)+			
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This being a conditional marketing a ufforization and pursuant to Article 14(7) of AppLation (BC)-lie 728/2004, the HAH shall complete, within the stated timeframe, the following measures: (

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Together with the low taxis ty of assembland the band to fits or al dasing regimen, the band trak belones to considered gestive. ( b) -trialitally that the applicant will be able to provide comprehensive data

The applicant will provide further comprehensive clinical data to confirm efficacy and aafety of ixazomb-in die proposed indexton. Here specifically die Applicant will provider?

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Annexes

#### 1. -- Reporteurs initial Assessment Report dated 6-November 2015

- 2. -+ Con-Report Euro Initial Assessment Report dated -12 November 20151
- 3. --- PRAC assessment every lev, a degted by -PRAC en-3-Desember-20131
- 4. -+ Consolidated-Ust-of-Questions-as-agreed-by-the-OnMPon-17-December-2015-1
- 5. -+ Consolidated Upt of Outstanding Jacque as careed by the OHMP on 25 Poblacy 20151
- → Jeint Reports w/Ce Reports w/ RAC Reports w Assessment Report on the responses provided by the apphaset, dated -15-March -2015.7
- 8. Second-consolidated-United Outstanding Sauce as a gread by the CHNP-on-1-Apri-20151
- → Joint Reporter/Co-Reporter/RACReporter Assessment Reporter Operaporter provided by Reappleart, deted-11-May 2018.1
- 10.--- Reported 's remained on assessment report dated 21. August 2018
- 11.--- Correspondeur's assessment-report dated 19 August 20101 12.-- Reporteurs Joint Assessment Report dated 31 August 20165

•Appendix¶

- 1. -+ CHHP-AR-on-similarity-dated-15-September-2018 2. --- MAR detailed grounds for the remaining



### Challenges in benefit-risk assessment

- Approval of drugs in EU is based on concept of positive benefitrisk balance
- Weigh multiple measures of benefit and risk using subjective value judgments
- Need to balance multiple measures of benefit and risk, with uncertainty:
  - Statistical uncertainty (i.e., wide confidence intervals), especially with regard to favourable and unfavourable effects with low incidences
  - Uncertainty with regard to the clinical relevance of the observed effects sizes due to the lack of evidence on hard clinical outcomes
- Publicity about the reasons and rationale that play a part in decisions

Daniels N. Accountability for reasonableness. *BMJ*. 2000 Eichler HG, et al. Fifty years after thalidomide; what role for drug regulators? *Br J Clin Pharmacol* (2012)



### What has changed

- March 2008: EMA publishes a reflection paper on benefit-risk assessment methods with two main recommendations:
  - 1. Revise the benefit-risk balance section of the CHMP Assessment Report (AR) template
  - 2. Research methodologies of benefit-risk balance
    - Involve experts in Decision Theory (L. Phillips, B. Fasolo)
    - Improve consistency, transparency and communication of B/R
    - Switch from "implicit" to "explicit" decision making



### The PrOACT-URL framework

- ⇒ A qualitative framework for structured decision making
- 1. Problem Determine the nature of the problem and its context
- 2. Objectives Establish objectives and identify criteria of favourable and unfavourable effects
- 3. Alternatives Identify the options to be evaluated against the criteria
- 4. Consequences Describe how the alternatives perform for each of the criteria
- 5. Trade-offs Assess the balance among favourable and unfavourable effects
- 6. Uncertainty Assess the uncertainty associated with the effects
- 7. Risk tolerance Judge the relative importance of the decision maker's risk attitude
- 8. Linked decisions Consider the consistency of this decision with past/future decisions



#### Benefit-risk assessment report template





### EMA Benefit/Risk Project

Descriptive methods: Effects Table

- Implemented in 2015
- Simple to build, useful compact display
- Can be generally applied, can be used as basis for quantitative methods

Quantitative methods: Multi Criteria Decision Analysis (MCDA)

- Require substantial resources/effort to build model
- Not used yet in actual decision-making
- "Pilot" studies on patient preferences

									mg		(See SPAR 12.4)
Freeurable Freeura		ě	SLEDAI % Emproved 5-4	Percentage of patients with a tileast 4 points' reduction in SLEDA3 <sup>3</sup>	100	٥	8	41	53	46	Approved only for patients with high
			SLEDAI % Improved > 6	Percentage of patients with more than 6 points' reduction in SLEDAI	100	٥	8	23	27	33	dises a sotivity. Uncertainties nemain a bout optimal treatment duration, maintenance doses, treatment holidays and rebound phenomenon.
		(cas)	PGA % no worse	Percentage of patients with no worsening in Physician's Global Assessment <sup>2</sup> (worsening - an Increase of less than 0.2 points)	100	٥	6	66	75	76	
	urable ecte		PGA Nean score	Overall mean change of PGA score from baseline for the study population	1.0	٥	Difference	0.44	0.46	0.45	
	1		BILAG A/B	Percentage of patients with no new BILAG <sup>2</sup> A/28	100	٥	<b>%</b>	69.0	75.2	70.1	
		adam of the second	CS Sparing	Percentage of patients that reduce d the dose of corticosteroids by more than 25% and to less than 7.5 mg/day	100	٥	"	123	17.5	20.0	The secondary effects are modest. Should they be considered in the
		9 8 8 8	Rana rata	Number of new BILAG A cases per patient year	٥	5	Number	3.51	2.66	2.90	overall benefit-rick balance?
			QoL	Mean change in the lotal score of SF 26 (Short Form)	٥	100	Difference	15	2.4	2.7	
	- te		Potential SASe	Potential for developing tumpur, a dverse interactions with vacches and AS on prepriancies	100	٥	3udge ment	100	٥	90	The mechanism of action could increase potential
	- now	ti at	Infections	Proportion of patients with serious infections that are life-threat ening	٥	10.0	<b>%</b>	52	5.2	6.6	for developing Infections
	5	•	San stilvity Residion	Proportion of patients with hypersensitivity reactions at any time in the study	٥	2.0		0.10	0.40	1.30	





# Why the reluctance?

Against	In favour
The doctor (expert/regulator) knows best	Impact of different stakeholders input (e.g., from patients) can be explored
Highly subjective; "unscientific"	No more subjective than any intuitive approach; subjectivity is handled explicitly
	Minimise bias of intuitive approaches
Require more effort; words are better than numbers; why change	Easy to update; numbers are clearer than words
Does not reflect mental process	Intuition can lead to error and bias
"Black box"	Easily understood, transparent
High precision is unattainable	Uncertainty can be managed explicitly
Oversimplification ("single number")	A single number summary is an abuse of the model
The authority of the decision-makers will be questioned	Regulator's decisions can be scrutinised

L. Phillips "Benefit-Risk Modelling of Medicinal Products: Methods and Applications" Benefit-Risk Assessment in Pharmaceutical Research and Development. CRC Press, pages 91-93.



### ICH<sup>\*</sup>guidance on B/R assessment

- Avoids advocating for or against specific methodologies for benefit-risk assessment
- "Descriptive" approach generally appropriate
- "Quantitative" approaches encouraged, without specifying a single method for this
- Special situations

\* International Council for Harmonisation of Technical Requirements for pharmaceuticals for Human Use

http://www.ich.org/fileadmin/Public\_Web\_Site/ICH\_Products/CTD/M4E\_R2\_Efficacy/M4E\_R2\_ 19Step\_4.pdf



### The role of industry

- Significant research in the area over many years
- Number of methods developed



#### IMI PROTECT Work Package 5

• Have not found their way in regulatory submissions



### Possibilities for regulatory guidance

- Scientific advice working party (SAWP) is a multidisciplinary group, comprised of members from different scientific committees of the EMA
- Integrated view on aspects such as
  - quality relating to the development of medicinal products;
  - non-clinical and clinical safety and efficacy relating to the development of medicinal products;
  - the significant benefit of orphan medicinal products;
  - MCDA?



### EU experience so far

- Only one SA request with questions on utility of MCDA in upcoming application
- Efforts to standardise evaluation of B/R were welcome by SAWP
- Questions on how parameters included in the model were weighted
- Consideration for patient as well as expert opinion
- Sensitivity analysis necessary



### Conclusions

- Important achievements over the last decade
  - Similar descriptive frameworks used by regulators
  - More transparency about the decision
- What role for quantitative approaches?
  - Aversion to quantitative approaches but the environment is changing
  - Openness to explore use of patient preference information
- How to support change?
  - Better understanding of the methods and motivation
  - Exposure to more examples/applications



# Thank you for your attention

#### Further information

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