EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Modelling to support Benefit/Risk assessment – Will it enhance our capability and improve transparency?

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EMA Benefit-Risk Project

15 December 2010—Regulatory Science: Are regulators leaders or followers?

EMA Benefit-Risk Project (2009-2011)

Purpose

To develop and test tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products

Work Packages

1. Description of current practice ✓
2. Applicability of current tools and methods ✓
3. Field tests of tools and methods ongoing
   - Tafamidis
   - Ozespa
4. Development of tools and methods for B/R
5. Training module for assessors

Work Package 1 result

What is a benefit?

1. Everything good
2. Improvement in health state
3. Real-world effectiveness
4. Clinical relevance
5. Imp ... ess
6. Suff
7. Positive action of drug
8. Meets unmet medical need
9. Positive improvement in health state as perceived by patient
10. Safety improvement
11. Value compared to placebo
12. Change in managing patient

:

37. Statistically significant effect

37

What is a risk?

1. All that is negative
2. Ad
3. Re
4. Ki
5. Si
6. Se ... s
7. Bad effects

12. Frequency of side effects

:

51. Potential or theoretical risks

51

Why this longer and more heterogeneous list?

Legislation might be a reason
Article 1 of the Directive 2001/83/EC, ¶28

What is a benefit?

- "positive therapeutic effect"

What is a risk?

- "any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health" as well as "any risk of undesirable effects on the environment".
- Risk is ... any risk!

Consider a new heart attack drug

"There is a risk this drug won't lower your risk and there are risks from taking the drug."

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Risk 1: possibility you are a non-responder

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Risk 1: possibility you are a non-responder

Risk 2: your probability of a heart attack

Consider a new heart attack drug

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Risk 1: possibility you are a non-responder

Risk 2: your probability of a heart attack

Risk 3: possible side effects

Consider a new heart attack drug

"There is a risk this drug won't lower your risk and there are risks from taking the drug."

Risk 1: possibility you are a non-responder

Risk 2: your probability of a heart attack

Risk 3: possible side effects

Which of these risks are 'balanced' in a regulator's benefit-risk assessment?

Clarifying the meaning of ‘benefit’ and ‘risk’

Favourable Effects	Uncertainty of Favourable Effects
Unfavourable Effects	Uncertainty of Unfavourable Effects

EMA Guidance Document
Day 80 Assessment Report (10/09)

V. BENEFIT RISK ASSESSMENT

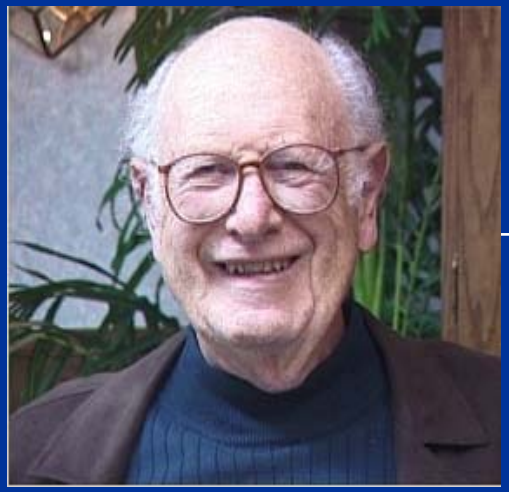
1. Describe beneficial effects
2. Identify main sources of uncertainty
3. Describe unfavourable effects
4. Identify uncertainties in the safety profile
5. Describe if favourable effects with their uncertainties outweigh the unfavourable effects with their uncertainties

Work package 2: Review of methods and approaches for benefit/risk assessment

- 3 qualitative and 18 quantitative approaches
- 3 approaches quantify effects *and* uncertainties
  - Bayesian statistics (for revising beliefs in light of new data)
  - Decision trees/influence diagrams (for modelling uncertainty)
  - Multi-criteria decision analysis (for modelling B/R trade-off)
- 5 other approaches for supplementary role
  - Probabilistic simulation (for modelling effect uncertainty)
  - Markov processes and Kaplan-Meier estimators (for health-state changes over time)
  - QALYs (for modelling health outcomes)
  - Conjoint analysis (for assessing trade-offs among effects)

Preparing for WP3

- LSE student projects, summer 2010
  - Acomplia: Weight management (MCDA + decision tree)
  - Sutent: GIST (decision tree + Markov model)
  - Tyverb: Advanced breast cancer (MCDA + probabilistic simulation)
  - Cimzia: Rheumatoid arthritis (MCDA + probabilistic simulation)
- Confirmed potential for models to clarify the benefit/risk balance based on information held by the EMA



"The spirit of decision analysis is divide and conquer: decompose a complex problem into simpler problems, get one's thinking straight on these simpler problems, paste these analyses together with logical glue, and come out with a program of action for the complex problem"

(Howard Raiffa 1968, p. 271)

Case study:Acomplia

active substance: rimonabant 20 mg

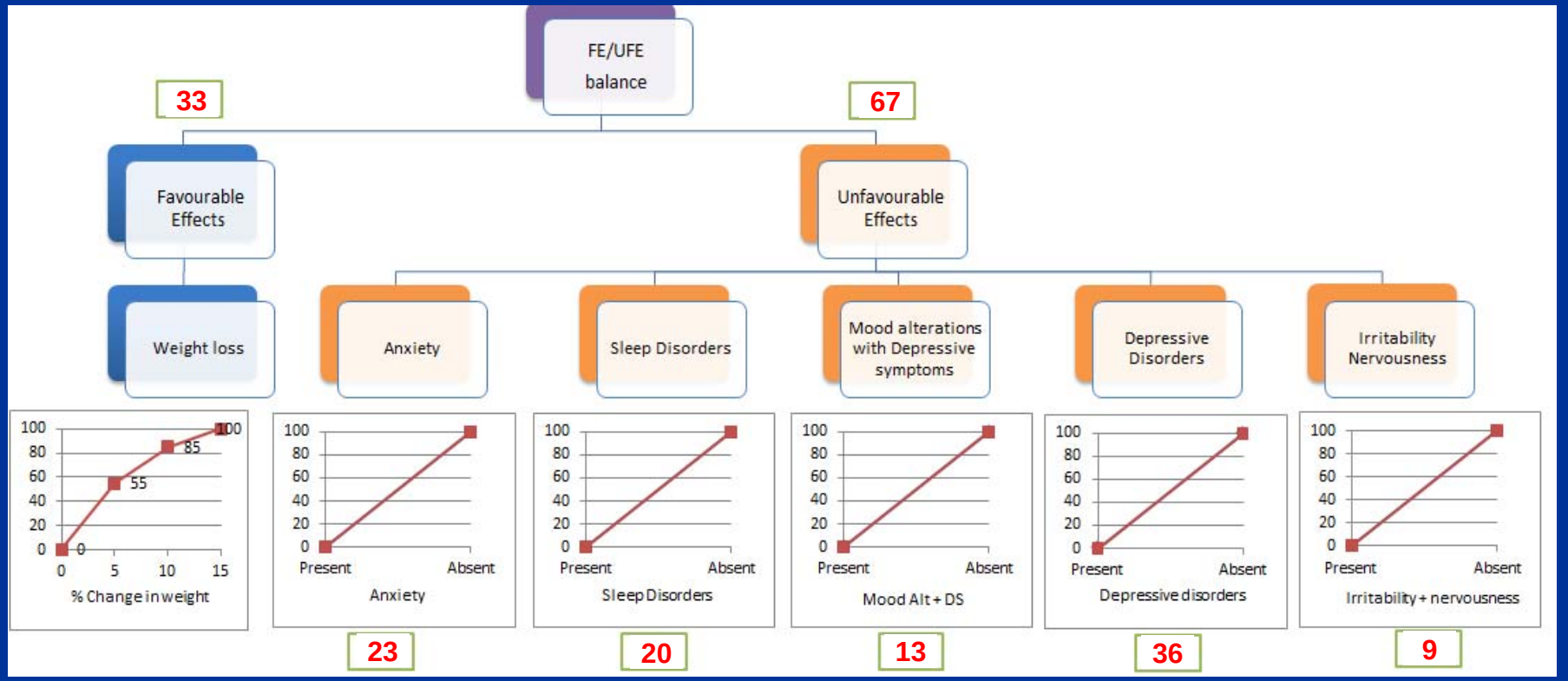
Proposed indications:

- Management of multiple cardiovascular risk factors
- Weight management
- Type 2 diabetes
- Dyslipidaemia
- Smoking cessation

- 19 Jun 2006: approved for obesity and over-weight patients.
- 16 Jan 2009: marketing authorisation withdrawn in light of post-approval data on the risk of psychiatric adverse reactions

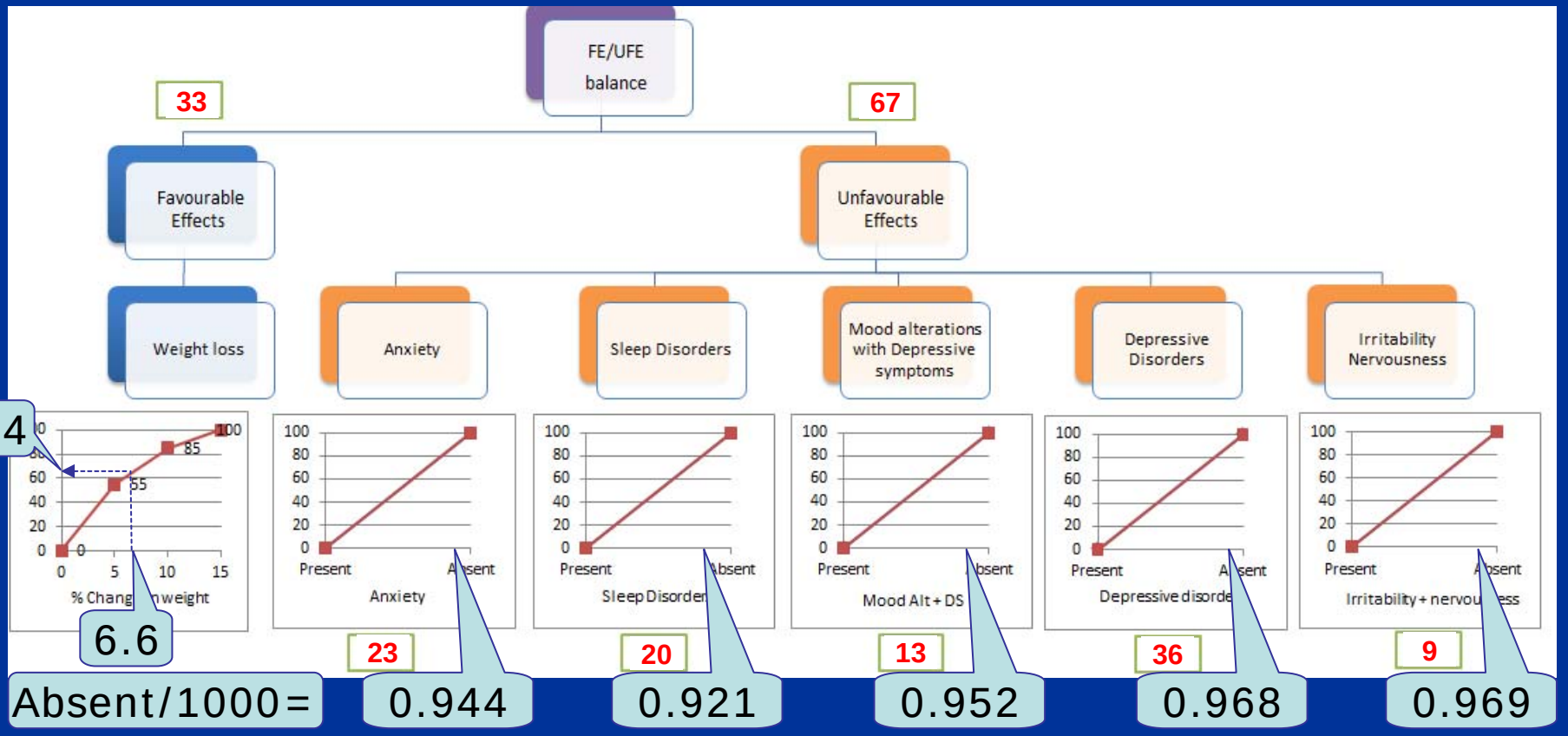
Multi-criteria decision analysis (MCDA) value tree with value functions and weights

Calculating overall FE/UFE balance
1. Normalise weights so sum = 100

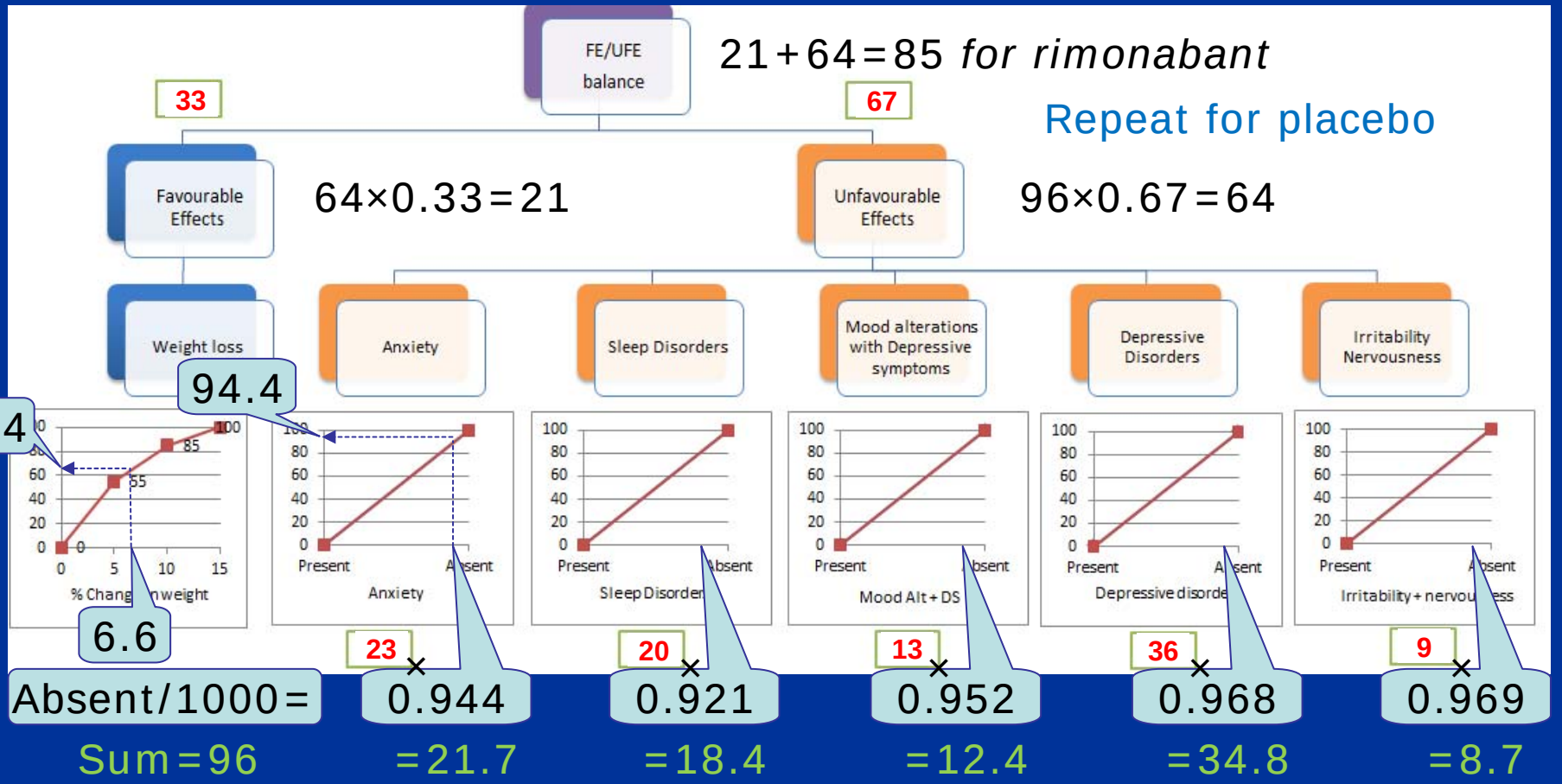


The perfect drug: 15% weight reduction, no side effects: Score = 100

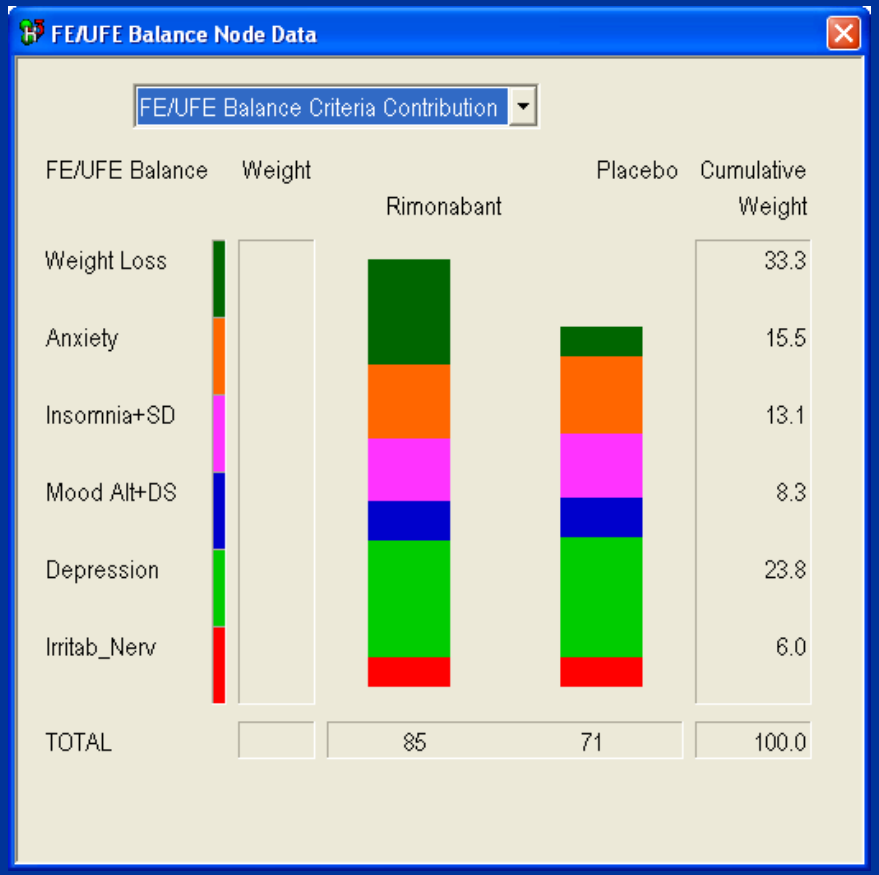
Calculating overall FE/UFE balance
2. Score rimonabant



Calculating overall FE/UFE balance
3. Multiply scores by weights



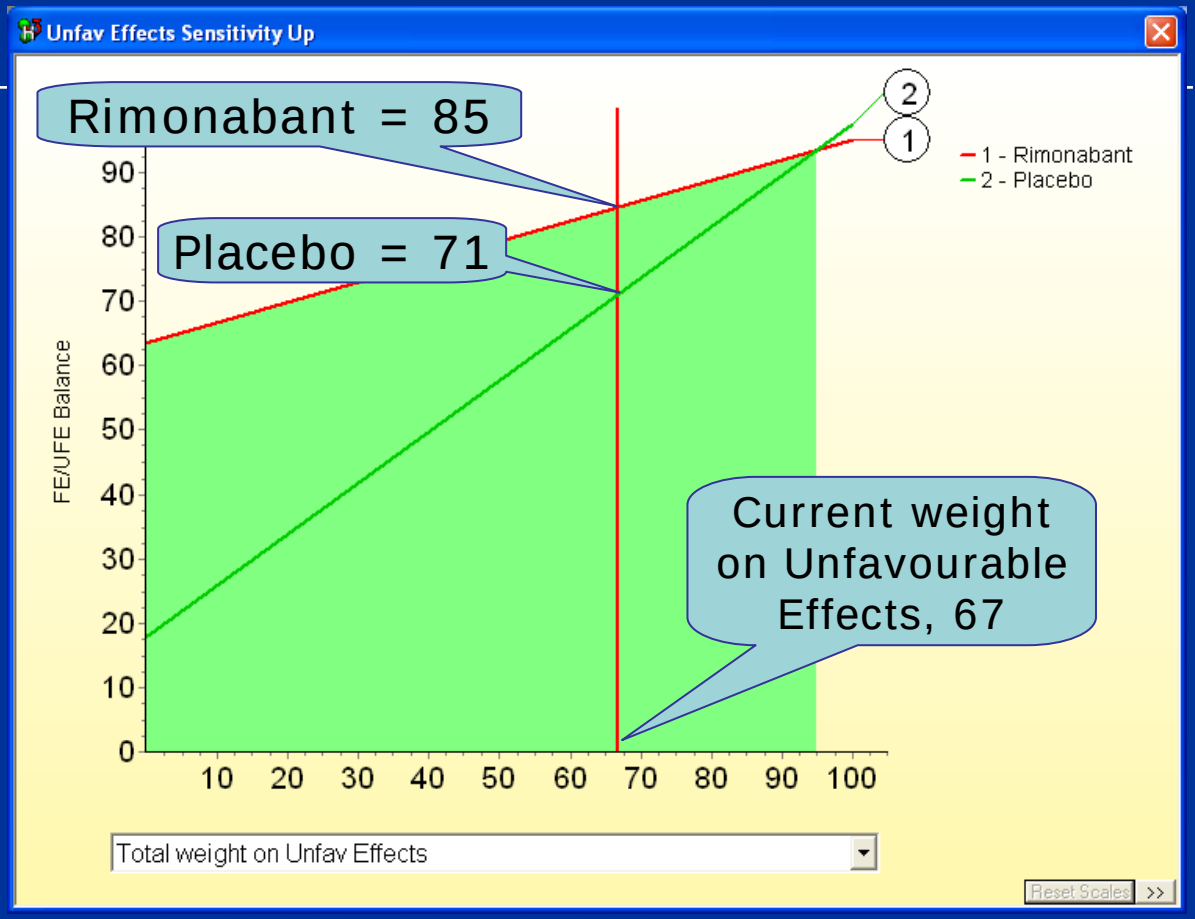
Overall results as stacked bar graph



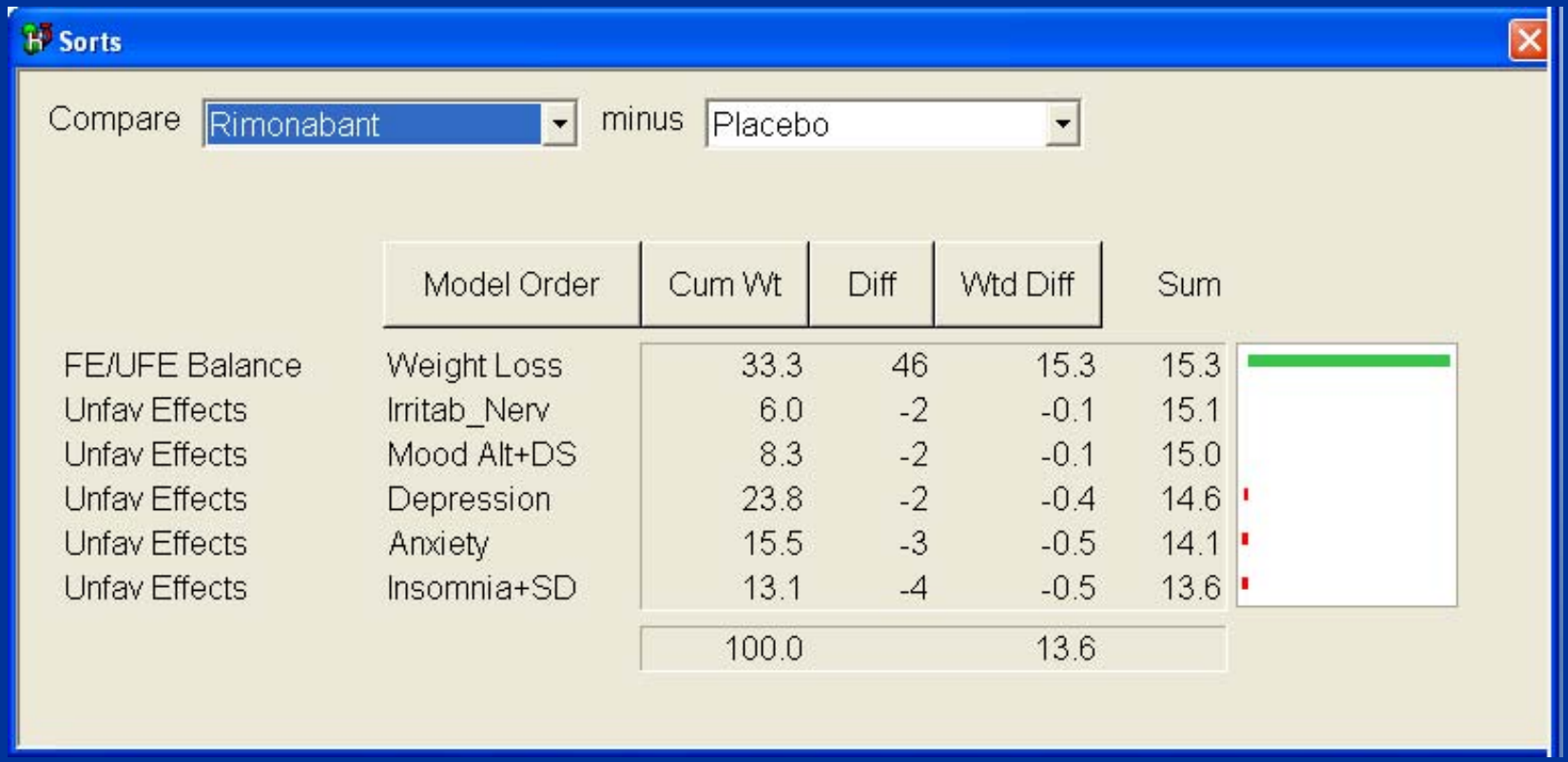
- Rimonabant better than placebo for weight loss
- Rimonabant very slightly worse for side effects
- This result from data in the public assessment report

Is the result sensitive to the weights on the effects?

A substantial increase in the weight on Unfavourable Effects would be required for the Placebo to be at most just slightly preferred.



Compare rimonabant with placebo

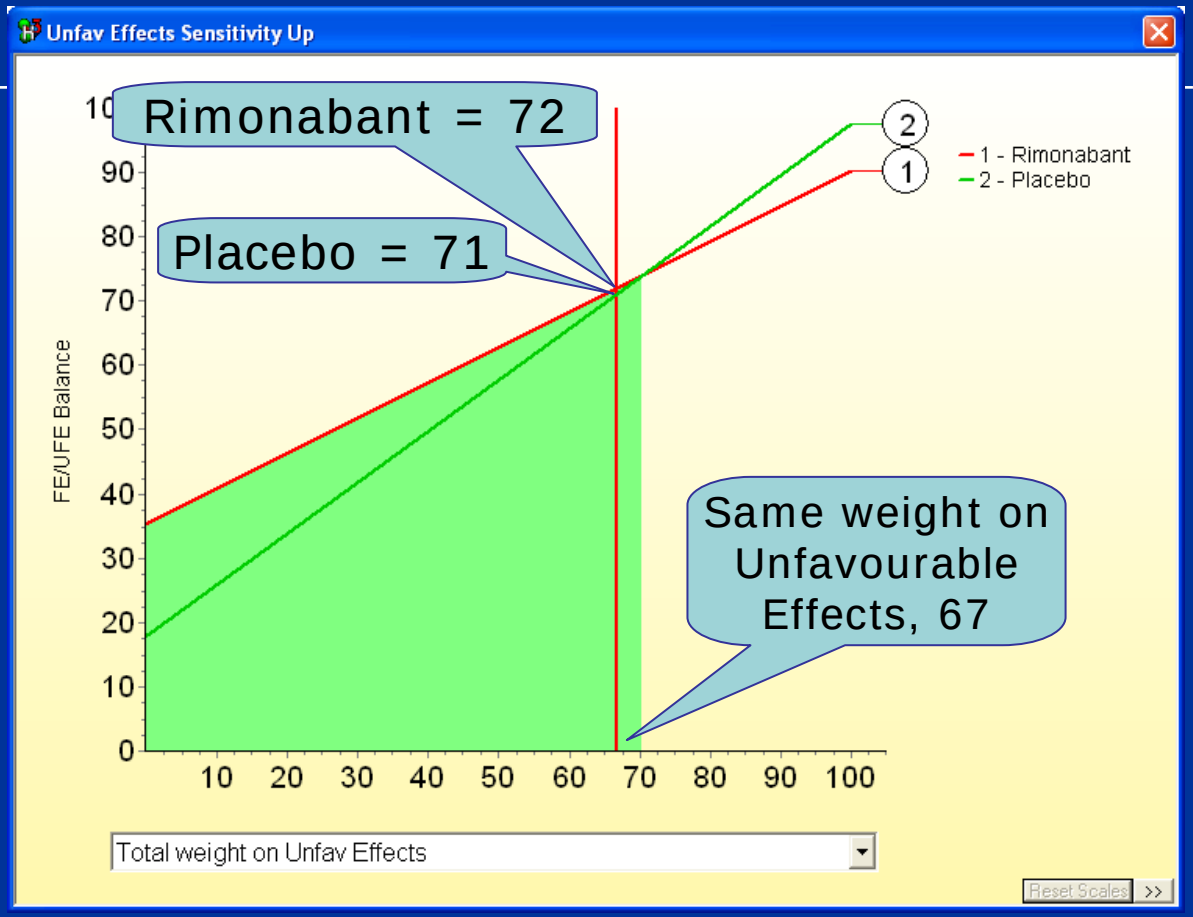


	Model Order	Cum Wt	Diff	Wtd Diff	Sum
FE/UFE Balance	Weight Loss	33.3	46	15.3	15.3
Unfav Effects	Irritab_Nerv	6.0	-2	-0.1	15.1
Unfav Effects	Mood Alt+DS	8.3	-2	-0.1	15.0
Unfav Effects	Depression	23.8	-2	-0.4	14.6
Unfav Effects	Anxiety	15.5	-3	-0.5	14.1
Unfav Effects	Insomnia+SD	13.1	-4	-0.5	13.6
		100.0		13.6	

Post approval: new evidence of psychiatric side effects

Double all proportions of unfavourable effects.
Halve weight-reducing effect.

Now rimonabant looks only marginally better than the placebo.



Compare rimonabant with placebo

Sorts

Compare Rimonabant minus Placebo

	Model Order	Cum Wt	Diff	Wtd Diff	Sum
FE/UFE Balance	Weight Loss	33.3	18	5.8	5.8
Unfav Effects	Irritab_Nerv	6.0	-5	-0.3	5.5
Unfav Effects	Mood Alt+DS	8.3	-7	-0.5	5.0
Unfav Effects	Depression	23.8	-5	-1.1	3.8
Unfav Effects	Anxiety	15.5	-9	-1.4	2.5
Unfav Effects	Insomnia+SD	13.1	-12	-1.6	0.9
		100.0		0.9	

What did we learn?

- The model confirmed the original approval of Acomplia
- The revised model, with new data, confirmed the withdrawal of the drug
- The model made the reasoning explicit in both cases
- Sensitivity analyses confirmed for both models that it is the *combination* of unfavourable effects that could tip the benefit-risk balance.
- The MCDA model can deal with the impacts of favourable and unfavourable effects, and with their uncertainties

Will group-based B/R modelling enhance our capability and improve transparency?

- Experience to date (with Tafamidis & Ozespa)
  - Helps to decompose the B/R assessment into relevant components
  - Aids exploration of different perspectives and values, and of uncertainties, for their effects on the B/R balance
  - Helps the group to combine data about values and uncertainties into an overall B/R balance
  - Facilitates group discussion
  - Forwards Day-80 thinking about the B/R balance
  - Can accommodate quality considerations

Two questions

Do you think that quantitative benefit-risk modelling will enhance our capability and improve transparency?

What might be the implications for adopting quantitative benefit-risk modelling as a key aspect of regulatory science?

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THANK YOU!