EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Value of Information: applying decision theory

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EMA Benefit-Risk Project

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EMA Benefit-Risk Project (2009-2011)

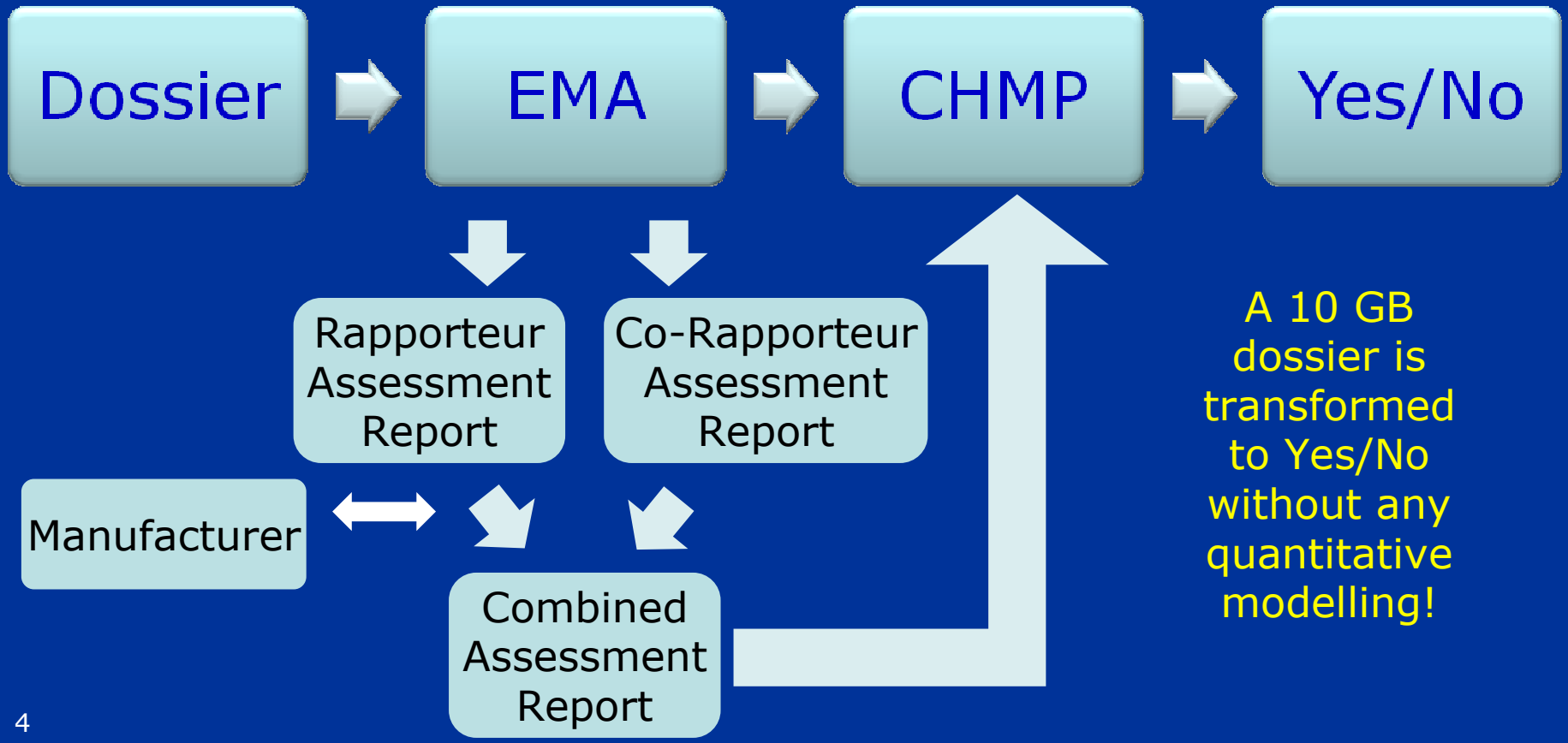
Purpose

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
   - LSE MSc students modelled four drugs ✓
   - 5 drugs for European Agencies, 1 more to go ongoing
4. Development of tools and methods for B/R ongoing
5. Training module for assessors

WP1: Current practice (approximately!)



A 10 GB dossier is transformed to Yes/No without any quantitative modelling!

WP1: Meaning of benefit and risk

What is a benefit?

1. Everything good
2. Improvement in health state
3. Real-world effectiveness
4. Clinical relevance
5. Improvement in illness
6. Suffering reduced
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

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37. Statistically significant effect

What is a risk?

1. All that is negative
2. Adverse events
3. Reduction in quality
4. Kinetic interactions
5. Side effects
6. Serious adverse effects
7. Bad effects
8. Danger for the patient
9. Tolerance of a drug compared to serious side effects
10. Harm
11. Severity of side effects
12. Frequency of side effects

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51. Potential or theoretical risks

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."

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

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

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

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

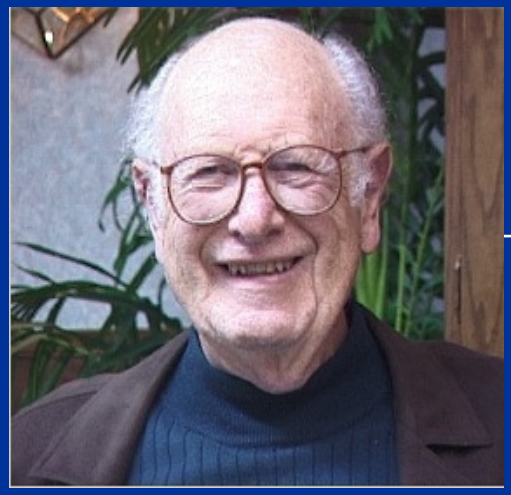
EMA Guidance Document
Day 80 Assessment Report (10/09)

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

WP2: 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)



"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)

WP3: Case study - Acomplia

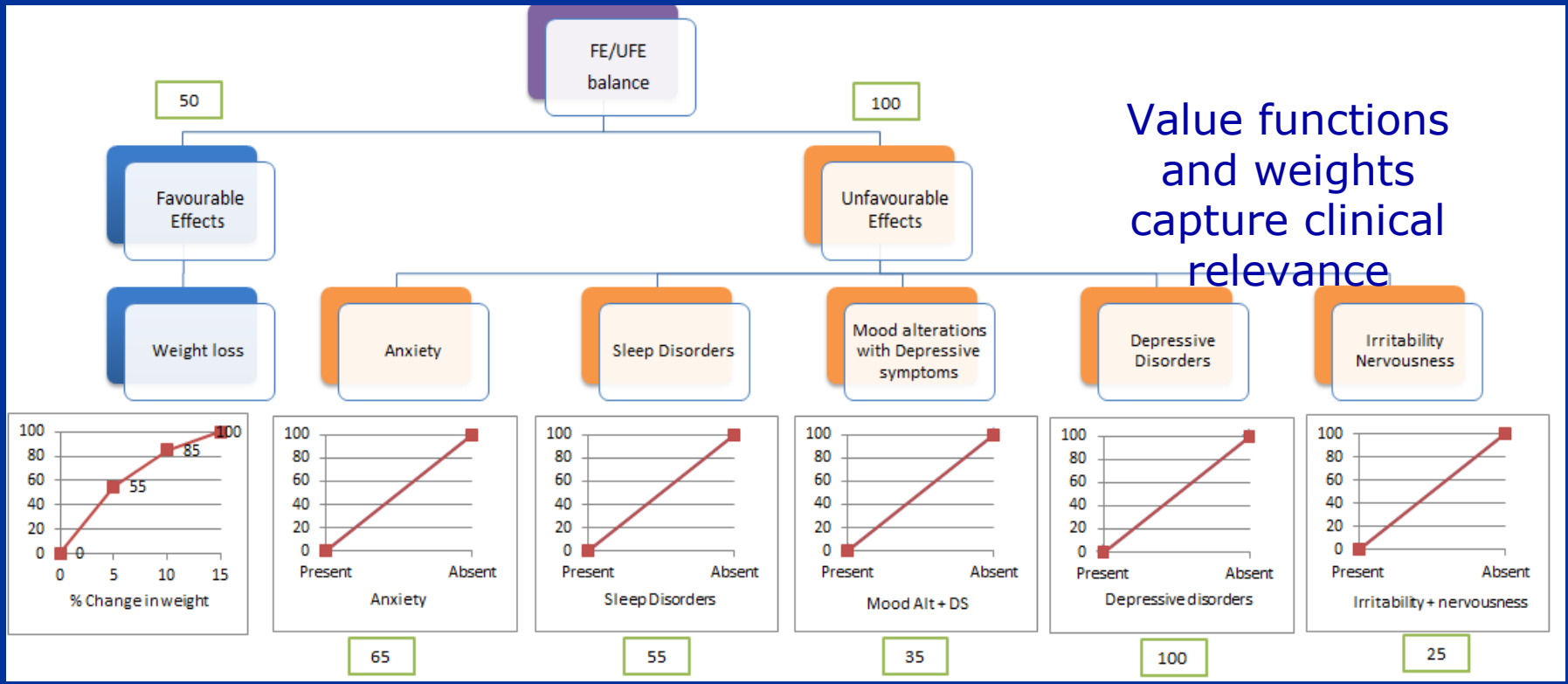
active substance: rimonabant 20 mg

Proposed indications:

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

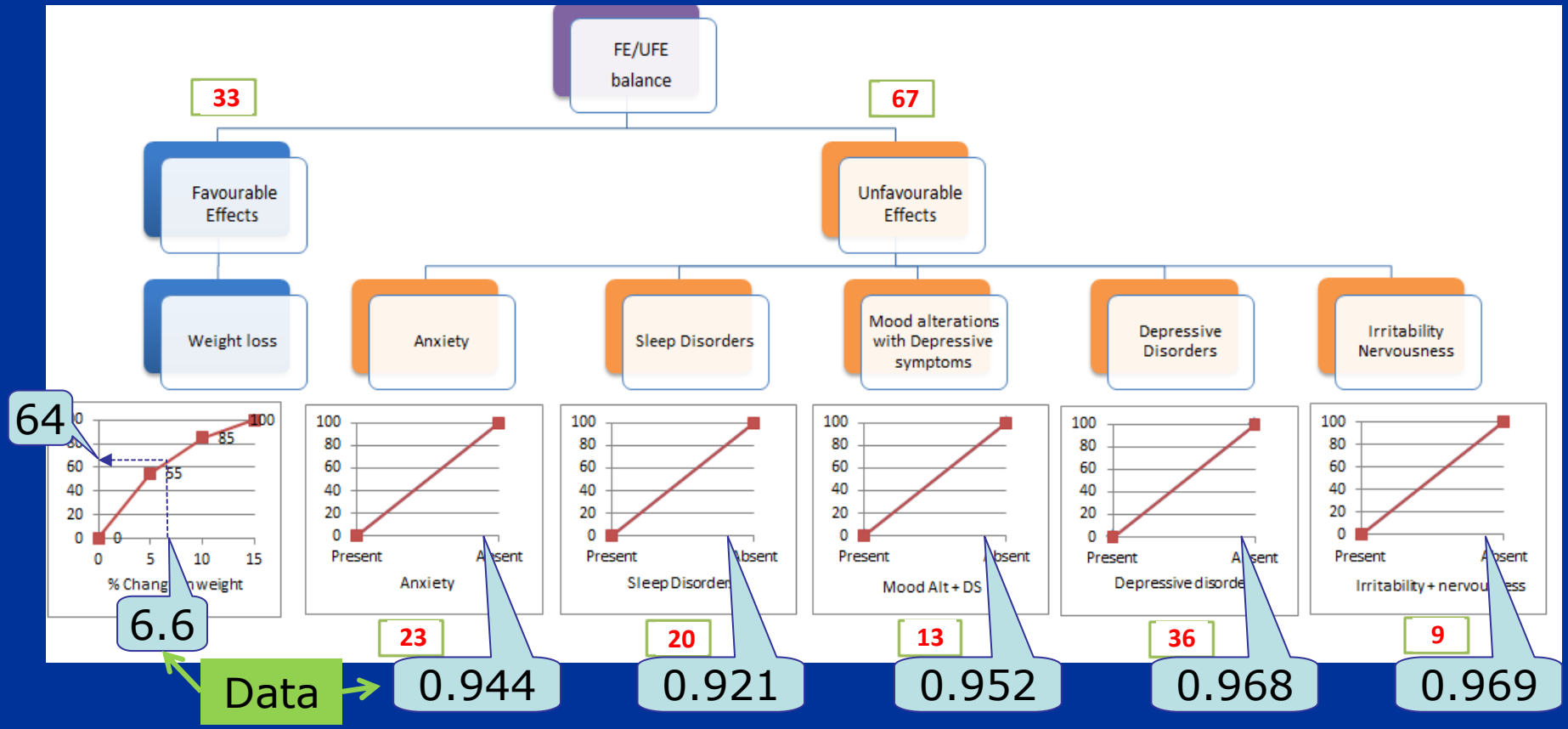
- 19 Jun 2006: approved for obesity and over-weight patients.
- 16 Jan 2009: marketing authorisation withdrawn in light of post-approval data on the risk of psychiatric adverse reactions

Decision analysis value tree

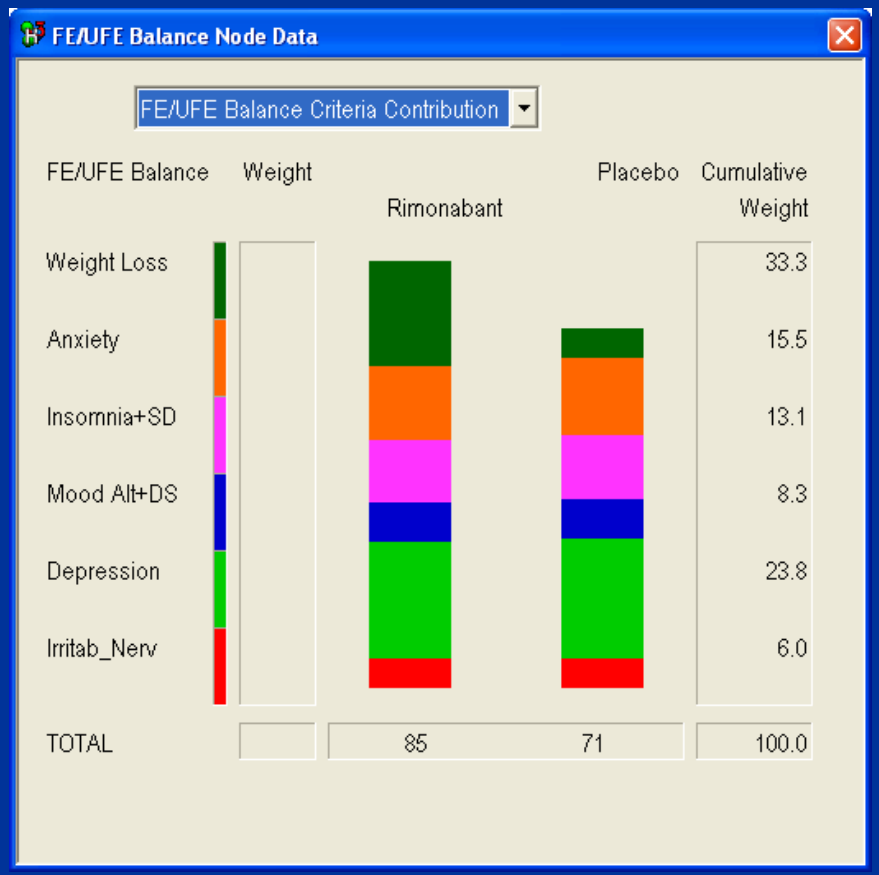


Value functions and weights capture clinical relevance

Data input and translation to preference values



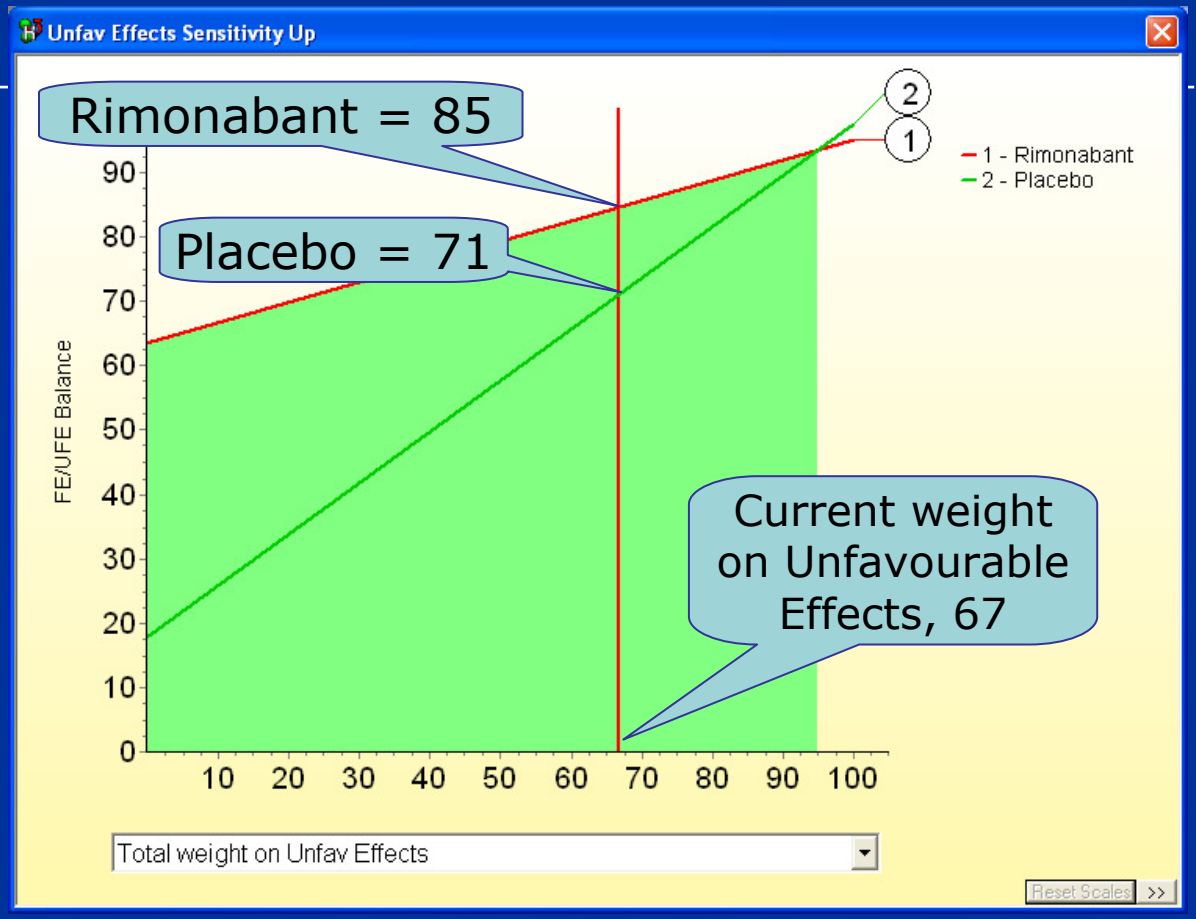
Overall results as stacked bar graph



- 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

Sorts

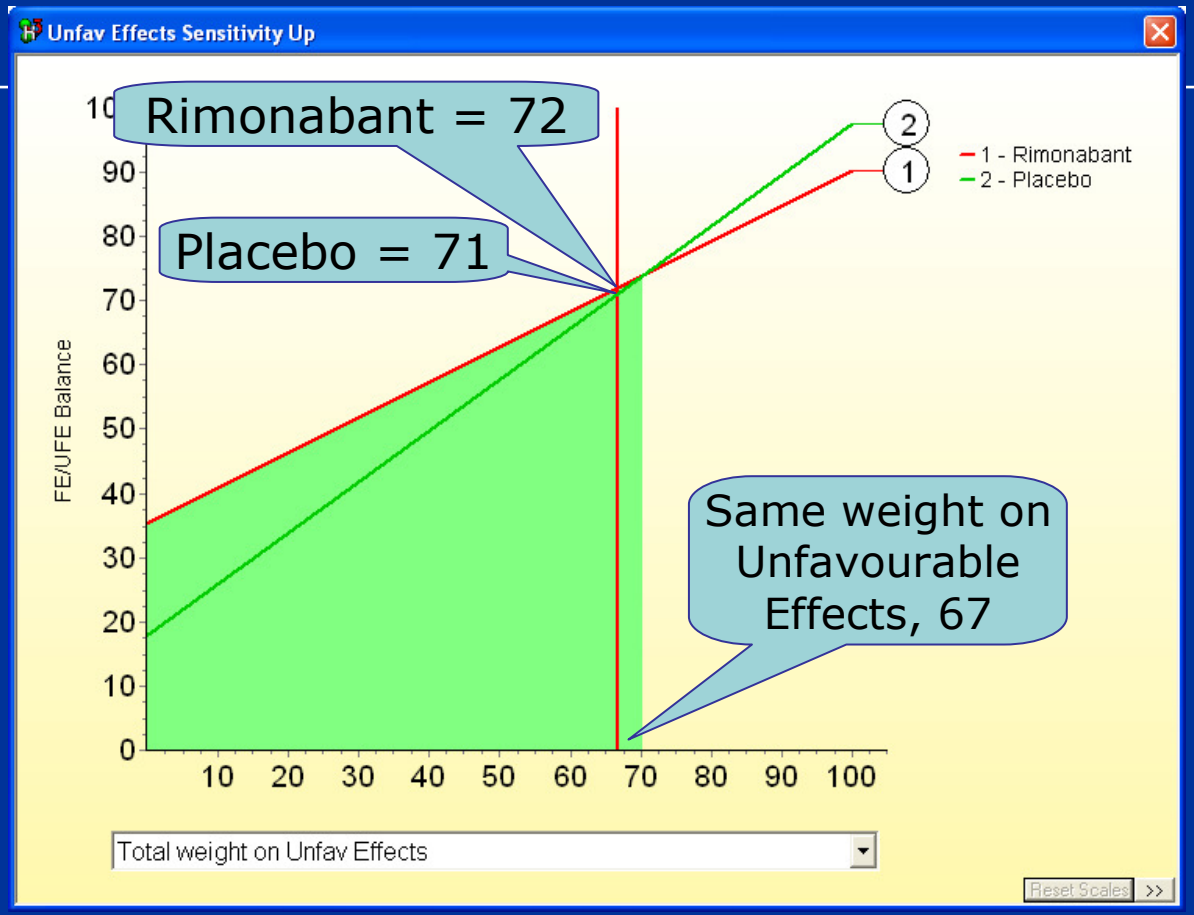
Compare Rimonabant minus Placebo

	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.

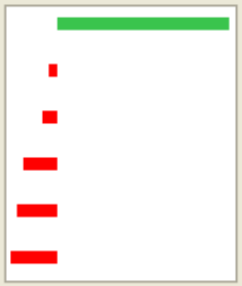


Compare rimonabant with placebo

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 decision analysis model can deal with the impacts of favourable and unfavourable effects, and with their uncertainties

Implications for policy deciders

- Evidence-based decisions require judgements to translate data into clinical value
- Current approaches to decision making are ill-defined, fragmented and opaque
- Patients' values are insufficiently represented
- Industry, regulators, health technology assessors and prescribers could improve transparency, communicability and quality by adopting quantitative modelling of benefit-risk

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THANK YOU!