IMI Work Package 5: Report 1:b:ii Benefit - Risk

Wave 1 Case Study Report: Ketek® (telithromycin)

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28th May 2013	Shahrul Mt-Isa	Empty section 6.1.7 Risk Awareness was removed and subsequent sections renumbered accordingly.

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Glossary

BRAT	Benefit Risk Action Team
BRR	Benefit Risk Ratio
CHMP	Committee for Medicinal Products for Human Use
DCE	Discrete Choice Experiment
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
INHB	Incremental Net Health Benefit
MCDA	Multi Criteria Decision Analysis
MTC	Mixed Treatment Comparison
NCB	Net Clinical Benefit
NNH	Number Needed to Harm
NNT	Number Needed to Treat
PhRMA	Pharmaceutical Research and Manufacturers of America
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PSM	Probabilistic Simulation Methods
QALY	Quality-Adjusted Life-Years
Q-TWiST	Quality-adjusted Time Without Symptoms and Toxicity
RCT	Randomised Controlled Trial
SMAA	Stochastic Multicriteria Acceptability Analysis
WP5	Work Package 5 (of PROTECT)

1 Introduction and Background

This report details a benefit-risk case study for Ketek (telithromycin) as part of the IMI PROTECT Work Package 5.

On 9 July 2001, the European Commission granted Aventis Pharma a marketing authorization for Ketek for treatment of the following infections: mild to moderate community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis (AECB), and acute sinusitis (ABS) in patients of 18 years and older, as well as tonsillitis/pharyngitis caused by Streptococcus pyogenes in adults and adolescents, as an alternative when beta-lactam antibiotics are not appropriate.

Throughout the year 2006, the CHMP reviewed relevant safety data on Ketek and asked the Marketing Authorisation Holder to submit comprehensive safety reviews, including updated analysis on hepatic adverse reactions, a review of the benefit-risk balance in each of the therapeutic indications and comparative data from clinical trials with telithromycin compared to other antibiotics. On the 12 February 2007, FDA authorised a new Ketek labelling (i.e. removal of the indications ABS and AECB from the labelling, and an update of safety parts including a contraindication in myasthenia gravis). During the January 2007, these concerns were discussed at CHMP and a request for comparative data from the MAH holder to EMA was made.

Compared to other macrolides, Ketek seems to be associated with a somewhat different risk profile, i.e. adverse reactions as eye disorders, which sometimes are of severe nature, and serious adverse reactions as aggravation of myasthenia gravis, loss of consciousness and acute liver failure. Altogether, these adverse reactions constitute a significant risk which could have impact on the approved therapeutic indications.

Currently registered treatments by indication are:

1. CAP: Amoxicillin, Clarithromycin, Trovafloxacin,
2. AECB: Amoxicillin-clavulanic acid, Cefuroxime, Clarithromycin, Azithromycin
3. ABS: amoxicillin-clavulanic acid, and cefuroxime.
4. TP: Penicillin, clarithromycin.

Section 2 of the report details the aims of the case study and the key questions to be addressed. Section 3 gives an overview and justification of the methods used as well a description of the dataset used in the analyses. Section 4 describes the results from applying the various methods and Section 5 critiques the methods with section 6 giving overall conclusions and recommendations.

2 Aim and Objectives

The objective of this case study is to assess the feasibility and suitability of selected approaches for benefit-risk assessment of drugs by the regulator, using Ketek antibiotic as an example. The selected benefit risk methods will be tested using data available from the EMA/CHMP EPAR product information and scientific discussion, 2007.

2.1 Key questions to be addressed

Two potentially interesting questions are:

1. Should Ketek be given marketing approval at the time of first registration?
2. Is FDA justified in removing the indications ABS and AECB from the labeling in 2007

3 Methods

3.1 Justification of selection of benefit-risk approaches

PROTECT Work Stream B recommended 13 methodologies to be tested in the first wave of case studies. In this case study, we have considered the possibility of applying these approaches but it is not possible to apply every approach due to resource constraints.

Table 4.1.1-1: Benefit risk approaches included for testing in Ketek case study

Approach	Justification
PrOACT-URL	The qualitative framework PrOACT-URL form a base for most of the comprehensive frameworks, and will be used to prepare the case.
BRAT	BRAT shares features with PrOACT-URL and MCDA in the step-wise structure of the approach, but in contrast to PrOACT the BRAT approach has a formal way of presenting data in two options for each criterion. BRAT does not integrate benefit and risk into one tabular value as MCDA does.
MCDA	MCDA shares many features with PrOACT-URL, in its stepwise structure to frame the problem. Furthermore MCDA provides decision analytic modelling approach to quantitatively model the benefit risk balance
SMAA	SMAA is a natural extension for MCDA, which takes into account the uncertainty in data and in criteria weighting
PSM using BRR	The metric BRR is tested here together with the estimation technique PSM. BRR has many features similar to NNT/NNH and impact numbers and is equivalent to the ratio of NNT to NNH. BRR with PSM also show the feasibility and suitability of using visualisation- risk-benefit plane (RBP) and risk-benefit acceptability curve (RBAC)
Sarac's Benefit-Risk Assessment Methodology (SBRAM)	Several features of SBRAM are similar to PrOACT-URL, MCDA and the other framework approaches in its stepwise approach to structure the decision process. At the same time SBRAM has a unique way of evaluating data on each criterion.

Table 4.1.1-2: Benefit risk approaches excluded from testing in Ketek case study

Approach	Justification
NNT/NNH	In this case study it was chosen to test the metric indices BRR, which shares many features with NNT/NNH
Impact numbers	In this case study it was chosen to test the metric indices BRR, which shares many features with Impact numbers
QALY	It is difficult to define QALY in antibiotics use
Q-TWiST	It is difficult to define the states for Q-TWiST (also as QALYs)
INHB	It is difficult to define INHB in antibiotics use (also as QALYs)
MTC	Not indicated, as direct evidence are available
DCE	Not used because of limitation of resources

3.2 Overview and Analysis Approach

The benefit risk approaches used for the case study are chosen to test methodologies which embrace a large variety of features and accommodate the expertise of the case study group, which include previous experience with BRAT, MCDA, SMAA, BRR, SPM and SBRAM. All benefit risk analysis on Ketek versus comparators was made with the perspective of the regulatory agencies, at a time point where the market authorisation after 6 year was re-evaluated, and indication restricted.

PhRMA BRAT & PrOACT-URL: The Benefit Risk Action Team (BRAT) framework is a complete benefit-risk assessment method that does not calculate a single benefit-risk summary metric. Some steps are similar to MCDA, i.e. defining decision context and identifying outcomes, but the BRAT framework has more clinical emphasis and detail, incorporates custom-designed tabular and graphic (Value Trees and Forest Plots) summaries of data. PrOACT-URL form a base for most of the comprehensive frameworks and was used here to prepare the case study. A more detailed description of methods is available in Sections 4.1.1-4.1.2.

MCDA & SMAA: The Multi-Criteria Decision Analysis (MCDA) method integrates multiple benefit and risk-criteria as well as sensitivity analyses to test the robustness of the choice of the different weights for each attribute. MCDA approach is sufficiently comprehensive to enable the benefit-risk balance to be represented numerically (as a difference or a ratio) by incorporating the weighted value or utilities of favourable and unfavourable effects. SMAA is an extension of MCDA to include uncertainty in the decision analysis. SMAA analysis can build a model by using a distribution of data rather than a single value as in MCDA. SMAA also allows missing weights, rank weights or range of weights between each criterion, compared to MCDA which require explicit weight information upfront for the analysis. A more detailed description of methods is available in Sections 4.2.1-4.2.2.

Probabilistic Simulation (PSM) and Benefit Risk Ratio (BRR): PSM allows more complex benefit-risk model to be constructed taking into account various uncertainties in input values. PSM (via Monte Carlo Simulation) was used to explore the statistical uncertainty (distribution) in benefit-risk balance obtained from the methods above (i.e. BRR). A more detailed description of PSM and BRR is available in Sections 4.3-4.4.

Sarac's Benefit-Risk Assessment Methodology (SBRAM): The SBRAM consists of a framework similar to the other comprehensive frameworks. One of the steps in the framework is weighing of criteria. This will be done by the group performing the assessment. The step of scoring in the SBRAM will be done using MATLAB, and scoring charts will be presented in the appendix. The results of the analysis will be presented visually using tornado-like diagrams. A more detailed description of SBRAM is available in Section 4.5.

3.3 Objective Data

Data used in the assessments are from the European public assessment reports (EPAR), "product information" and "scientific discussion" (EMEA/H/C/354/A22/41, London, 30 Marts, 2007).

- Cure rates (benefit data) of Ketek and its comparators are from three phase III/IV clinical trials

- Incidences of cardiac AE, hepatic AE, visual AE, syncope from pooled phase III and VI clinical trials for Ketek and its comparator.

3.4 Subjective Data

Weighing of the different criteria was done within the project group.

4 Results

4.1 Descriptive Approach

4.1.1 PrOACT-URL

STEP	DESCRIPTION	INFORMATION SOURCES
PrOBLEM 1. Determine the nature of the problem and its context.	1a. The medicinal product The medical product is Ketex the active substance is Telithromycin. Telithromycis is a semi-synthetic derivative of erythromycin A belonging to ketolide antibiotic, a class related to macrolides. Telithromycin inhibits protein synthesis by interaction with domains II and V of the 23S ribosomal RNA of the 50S ribosome subunit. Furthermore, telithromycin is able to block the formation of the 50S and 30A ribosomal subunits. 1b. Indication(s) for use. EU authorization on 9th July 2001 Ketex is indicated for treatment of following infections In Patient of 18 years and older: • Community-acquired pneumonia, mild or moderate • Acute exacerbation of chronic bronchitis • Acute sinusitis In Patient of 12 years and older: • Tonsillitis/pharyngitis cause by Group A beta streptococci, as an alternative when beta lactam antibiotics are not appropriate FDA 12th Febuaray 2007 indication for Ketex is restricted to following In patients of 18 years and older: Mild to moderate community-acquired pneumonia (CAP) due to Streptococcus penumoniea, (including multi-drug resistant isolates, Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae, or Mycoplasma pneumoniae) The updated label includes a boxed warning and a contraindication stating that no one with myasthenia gravis should take Ketek. In addition, warnings were strengthened for hepatotoxicity (liver injury), loss of consciousness, and visual disturbances. The new label narrows the usage for Ketek by dropping two previously approved indications (acute bacterial exacerbation of chronic bronchitis due to Streptococcus pneumoniae, Haemophilus, influenzae, or Moraxella catarrhalis; and acute bacterial sinusitis due to	EMEA/H/C/354/A22/41,London, 30 Marts, 2007 EMEA 2001, CPMP/1014/01 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000354/WC500041893.pdf NDA 21-144/S-012 http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021144s012lbl.pdf

	Streptococcus pneumoniae, Haemophilus influenzae, Moraxella EMEA, 30th Marts 2007 indication for Ketex is restricted to following In patients of 18 years and older: • Mild to moderate community-acquired pneumonia (CAP) When treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin • Acute exacerbation of chroic bronchitis (AECB) • Acute sinusitis (ABS) In patients of 12 years or older and • Tonsillitis/pharyngitis (TP) caused by Streptococcus pyogenes, as an alternative when beta-lactam antibiotics are not appropriate in countries/regions with a significant prevalence of macrolide resistant S. pyogenes, when mediated by ermTR or mefA Introduction of a contraindication for patients with myasthenia gravis. This was previously introduced as a warning. 1c. The therapeutic area and disease epidemiology: Ketek is indicated in the treatment of community acquired Respiratory Tract infections. (CAP, AECB, ABS and TP) 1d. The unmet medical need: Beta-lactam agent and macrolides are commonly used for the treatment of community acquired RTI, but resistance against S. pneumoniae has reached significant levels in several European countries. The key organisms associated wth RTI are: • Streptococcus pneumoniae (including penicillin- and/or macrolide-resistant strains) • Haemophilus influenzae (including beta-lactamase-producing strains) • Moraxella catarrhalis (including beta-lactamase-producing strains) • Staphloccussus aureus • Streptoccus pyogenes In addition, atypical and intracellular pathogens such as: • Mycoplsama pneumoniae • Chlamydophila pneumoniae • Legionella pneumophila All these pathogens have been shown to be sufficiently covered by the spectrum of telithromycin Severity of condition: Community –acquired pneumonia is a RTI (respiratory tract infections) associated with a significant morbidity and	EMEA/H/C/354/A22/41, London, 30 Marts, 2007

	mortality. • 1 in 5 cases requires hospilisation • Mortality rate in outpatients <1% • Mortality rate in most severe cases requiring hospitalization is 10% Affected population: Patients' and physicians' concerns: Time frame for health outcomes: 1e. The decision problem: Does the benefits of Ketek outweigh the risk using the drug for the four indications community acquired pneumonis (CAP), acute bacterial sinusitis (ABS), acute exacerbation of chronic broncihtis (AECB) and tonsillitis/pharyngitis (TP) so that a market approval can be granted for one for more of the indications? If not are there any risk minimization measures which could be implemented, thus bringing the benefit risk balance to be positive, such as safety restrictions? Considering post-marketing observations on QTc prolongation and acute liver injury, is the benefit risk profile still considered positive? Again, if not could safety restrictions to the indications bring the benefit risk balance for ketek to be positive for one or more of the indications? By whom: The benefit risk assessments will be done with the perspective of the regulator (EMA/FDA), making decisions about granting, maintaining or refining marketing approval for Ketek Time frame: In 2001 the EU granted Ketek marketing authorisation for treatment for the following infection mild to moderate CAP, EACB, ABS in patients of 18 or older as well as TP caused by streptococcus pyogenes in adults and adolescents as an alternative when beta-lactam antibiotics are not appropriate. Throughout 2006 CHMP reviewed relevant safety data on Ketek. CHMP/EMA asked Marketing Authorisation Holder (MAH) to submit comprehensive safety reviews, including updated analysis on hepatic adverse reactions. In 2007 FDA ordered new Ketek labelling, where the indication ABS and AECH was removed, safety parts was updated including a contraindication in myasthenia gravis. In January 2007 CHMP requested the responses to the following questions to be provided be the MAH. • MAH should carry out a benefit risk evaluation for Ketek in all authorised indication – Comparative data from clinical trials with telithromycin compared to other antibiotics (such as erythromycin, clarithromycin, roxithromycin, amoxicillin/clavulanic acid)	EMEA/H/C/354/A22/41, London, 30 Marts, 2007 EMEA/H/C/354/A22/41, London, 30 Marts, 2007

2. Frame the problem.	for which data is available to MAH should be included in the evaluation. • In the context of the indentified risk that MAH should propose adequate Risk Minimization Measures whenever necessary • The time frame of the following benefit risk assessments will be at time of re-evaluation on Ketek authorisation by EMA in 2007. 2a. Whether this is mainly a problem of uncertainty, or of multiple conflicting objectives, or some combination of the two, or something else (e.g., health states' time progression). Compared to other macrolides, Ketek seems to be associated with a somewhat different risk profile, such as visual adverse events, syncope and acute liver failure, and also aggravation of myasthenia gravis. At the same time there are in some European countries a high *S.penumoniae* resistance to antibiotics especially in Southern Europe. The main problem in connection to the Ketek benefit risk assessment involves the different risk profile associated to Ketek compared to other macrolides and the potential effect of risk minimisation measures. 2b. The factors to be considered in solving the problem Sources and adequacy of data: Clinical efficacy data of telithromycin from 12 double-blind comparative trials and 4 open label noncomparative trials. Comparators The adverse event (AE) profile of telithromycin has been examined in 4780 telithromycin-treated subjects (2702 from comparative studies and 2078 from open label studies) and 2139 comparator-treated subjects in Phases III pivotal efficacy and safety studies. In addition 12159 subjects in the telithromycin treatment group of study A3014 (Phase IV study) were evaluated for safety. Presence of alternative treatments: Increasing resistance towards Beta-lactam agent and macrolides in several European countries	EMEA/H/C/354/A22/41, London, 30 Marts, 2007 IMI Protect WP5: Wave-1 Case Study Plan for B-R Assessment of Ketek, version 1.0 EMEA/H/C/354/A22/41, London, 30 Marts, 200 EMEA/H/C/354/A22/41, London, 30 Marts, 2007
OBJECTIVES 3. Establish objectives that indicate the overall purposes to be achieved. 4. Identify criteria for a) favourable effects b) unfavourable effects	3. The aim: to evaluate the benefit-risk balance for Ketek, with the use of safety and efficacy data obtained form clinical trials and cumulative post-marketing safety information from a regulators perspective. And to assess change in benefit-risk balance which could give reason for recommending restriction to the authorization. The benefit-risk evaluation will be done using BRAT, MCDA, SMAA, NNT/NNH, Impact numbers and PSM. 4. A full set of criteria covering the favourable: • Cure rate The clinical response was categorised as cure or failure. Evaluation of efficacy is evaluated based on sixteen phase III studies (12 double-blind comparative trials and 4 open label non-comparative trials)	IMI Protect WP5: Wave-1 Case Study Plan for B-R Assessment of Ketek, version 1.0 EMEA/H/C/354/A22/41, London, 30 Marts, 2007

	Community-acquired pneumonia (CAP) (Studies 3000, 3001, 3006, 3009) • 4 phase III double blind (A3001, A3006, A3009, A4003) • 4 Phase III open label clinical trials (A3000, A3009OL, A3010, A3012) • 3 Phase IV studies Acute sinusitis (ABS) • 3 Phase III trials (3002, 3005, 3011) • 3 Phase IV randomized controlled trials Acute bacterial exacerbation of chronic bronchitis (AECB) • 3 Phase III trials (A3003, A3007, A3013) • 4 controlled Phase IV trials Tonsillitis/pharygitis (TP) • 2 Phase III trials The primary analysis of efficacy was the per protocol analysis at post therapy/TOC (test of cure) of clinical outcome (PPc populations) in studies 3000, 3001, 3002, 3003, 3005, 3006, 3007 and 3009, and the per protocol analysis of bacteriological outcome (PP population) in studies 3004 and 3008 One controlled phase IV study tested PERSP at test of cure for telithromycin an Axithromycin and Cefuroxime. A full set of criteria covering the unfavorable effects: • Hepatic adverse events • Cardiac adverse events (including QTc prolongation) • Visual adverse events • Syncope • Treatment emergent adverse events (TEAEs) • Serious adverse events (SAEs) • The risk profile of telithromycin, including rare events of concern with antibiotics approved in the same indications, as been thoroughly examined with clinical trials, intensified monitoring, and postmarketing surveillance. The adverse event profile of telithromycin has been examined in 4780 telithromycin-treated (2702 from comparative studies and 2078 from open label studies) and 2139 comparator-treated subjects in phase III pivotal efficacy and safety studies. In addition, 12159 subjects in the telithromycin treatment group of study A3014 were evaluated for safety. Safety data presented in the EPAR are pooled per indication, all phase III studies together, all open label phase III together and all phase IV together.	EMEA/H/C/354/A22/41, London, 30 Marts, 2007
ALTERNATIVES 5. Identify the options to be evaluated against the	5a. Pre-approval:	

criteria.	5b. Post-approval: In this benefit risk analysis only two alternatives are identified • Ketek • Comparators Where comparators are taken as a single alternative which are standard treatment antibiotics, this is done since all safety data are pooled in the EPAR.	
CONSEQUENCES 6. Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects.	6. The consequences separately for each alternative on each criterion (except for the efficacy criteria cure rate, where the consequence is presented per study) see Appendix A: Data on Ketek from EPAR. Following benefit risk approaches will be tested using the Ketek case: • Benefit Risk Action Team (BRAT) • Multi-Criteria Decision Analysis (MCDA) • Stochastic Multi-criteria Acceptability Analysis (SMAA) • Probabilistic Simulation Method (PSM) Each benefit risk methodology include methods for evaluation the performance of drug and comparator, this is displayed in the following sections.	
TRADE-OFFS 7. Assess the balance between favourable and unfavourable effects.	7. The judgement about the benefit-risk balance: In 2001 CHMP judge that the benefit-risk balances for treatment with Ketek in CAP, ABS, AECB and TP was positive. 2007 FDA judge the balance to be negative for the indications ABS and AECB. At the same time CHMP that found the balance to be positive for the all four indication, provided that infections is caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin. In this case study several approaches are used to determine the balance between favourable and unfavourable effects, the results from each approach can be seen in the respective section on under results. • Benefit Risk Action Team (BRAT) • Multi-Criteria Decision Analysis (MCDA) • Stochastic Multi-criteria Acceptability Analysis (SMAA) • Probabilistic Simulation Method (PSM)	EMEA/H/C/354/A22/41, London, 30 Marts, 2007

UNCERTAINTY 8. Report the uncertainty associated with the favourable and unfavourable effects. 9. Consider how the balance between favourable and unfavourable effects is affected by uncertainty.	8. The basis for and extent of uncertainty in addition to statistical probabilities (e.g., possible biases in the data, soundness and representativeness of the clinical trials, potential for unobserved adverse effects) 9. The extent to which the benefit-risk balance in step 7 is reduced by considering all sources of uncertainty, to provide a benefit-risk balance, and the reasons for the reduction. See under each methodology analysis in result section • Benefit Risk Action Team (BRAT) • Multi-Criteria Decision Analysis (MCDA) • Stochastic Multi-criteria Acceptability Analysis (SMAA) • Probabilistic Simulation Method (PSM)	
RISK TOLERANCE 10. Judge the relative importance of the decision maker's risk attitude for this product. 11. Report how this affected the balance reported in step 9.	10. Any considerations that could or should affect the decision maker's attitude toward risk for this product (e.g., orphan drug status, special population, unmet medical need, risk management plan). • Medical need is covered by several other therapeutic options • Increasing infection by beta-lactam and/or macrolide resistant strains 11. The basis for the decision maker's decision as to how tolerable the benefit-risk balance is judged to be (taking into account stakeholders' views of risk?).	EMEA/H/C/354/A22/41, London, 30 Marts, 2007

LINKED DECISIONS 12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.	12. How this decision, and the value judgments and data on which it is based, might set a precedent or make similar decisions in the future easier or more difficult.	

4.1.2 Benefit Risk Action Team (BRAT) Framework

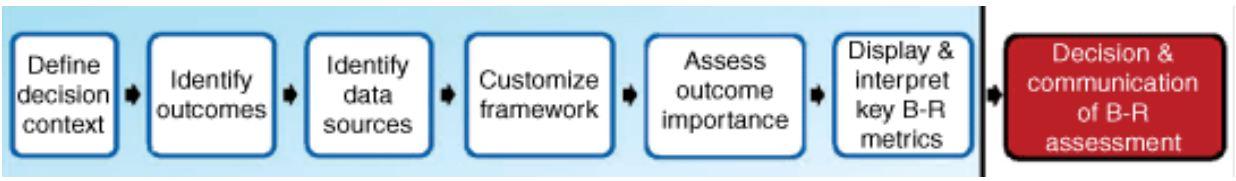
4.1.2.1 Introduction

The PhRMA BRAT Framework is a set of principles, processes and tools to help decision-makers select, organize, understand and communicate evidence for pharmaceutical benefit-risk decisions. The Benefit Risk Assessment Team Software Tool (BRAT Tool) is a prototype tool that allows users to generate the tabular and graphical displays in the published version of the PhRMA BRAT Framework. The purpose of the Tool is to enable users to generate value trees, key benefit-risk summary tables (KBRS tables) and forest plots as shown in BRAT publications [2, 3] and in the PhRMA BRAT User Guide.1

While not a limitation of the PhRMA BRAT Framework itself, the current BRAT Tool is limited to dichotomous (binary) endpoints on two treatments at a time. The purpose of the BRAT Tool is to automate the charting and visualization of numeric data related to two (2) different treatments (or treatment vs. placebo). All visualizations and related data and functions can be found on several visible worksheets (Tabs) as follows:

- Main - Main Menu - Primary interface for navigation and operation of the tool
- Value Tree - Used to define the outcomes (endpoints) for the benefit-risk assessment and how they are organized in categories
- Filters – For defining up to four categorical properties that can be used to filter the outcome data displayed in the visualizations
- Data - Where users enter and store numerical data for visualizations. Currently limited to dichotomous (binary) endpoints for two treatments.
- KBRS – Where users can create and customize Key Benefit-Risk Summary Tables
- Forest Plots - Allows creating and customizing two Forest Plot visualizations:
  Risk Difference Forest Plot
  Relative Risk Forest Plot
- Global Settings – Allows users to define the appearance of visualizations and general parameters used in the tool, including; names of treatments, value tree colours, and whether the data included are risks or rates
- Data Errors – List of error and warning messages caused by non-conformance with standards in the Data tab.
- Help – Where users can go to find technical and operational help for the use of the tool.[1]

Figure 4.1.2-1: Steps in the BRAT Framework[1,2]



4.1.2.2 Outcomes of Ketek Case Study

As outlined above, the BRAT Framework is an approach to benefit – risk analysis, based in decision analytic techniques. Users are encouraged to follow a structured framing process as described in the

BRAT publications[2,3] and are likely to benefit from an experienced facilitator/analyst when learning the process. The first step in the BRAT Framework is to provide the context for the analysis (including the disease or condition, the patient population, the time frame, and the stakeholder perspective). For this case study, the context was defined, as described in the introduction to the overall report.

The second step, identifying the outcomes of interest, is accomplished with the use of a value tree that is part of the BRAT Software Tool. The user completes two levels of the tree, naming the benefits and risks, and defining the measures of each. The user can designate outcomes of unknown relationship to the drug of interest (gray nodes), called "potential" benefit / risk categories or outcomes, and can designate nodes to be hidden, e.g., if data is not available or if there is a desire to display different views for different stakeholders. For this case study, the results of the Ketek analysis as reported in the EPAR Scientific Discussion were used.

For Step 3, identify data sources, entering the data into this value tree automatically begins to populate a data table that in turn will populate two other outputs in the software tool. Data can be from multiple sources, including clinical trials, observational studies, and publications. From this table, the user selects the data that will populate the Key Benefit Risk Summary Table (KBRS) (Step 4, customize framework), which can show risks for proportions of patients or rates in person-years. The denominator (1000 patients in the tables below) can be adjusted.

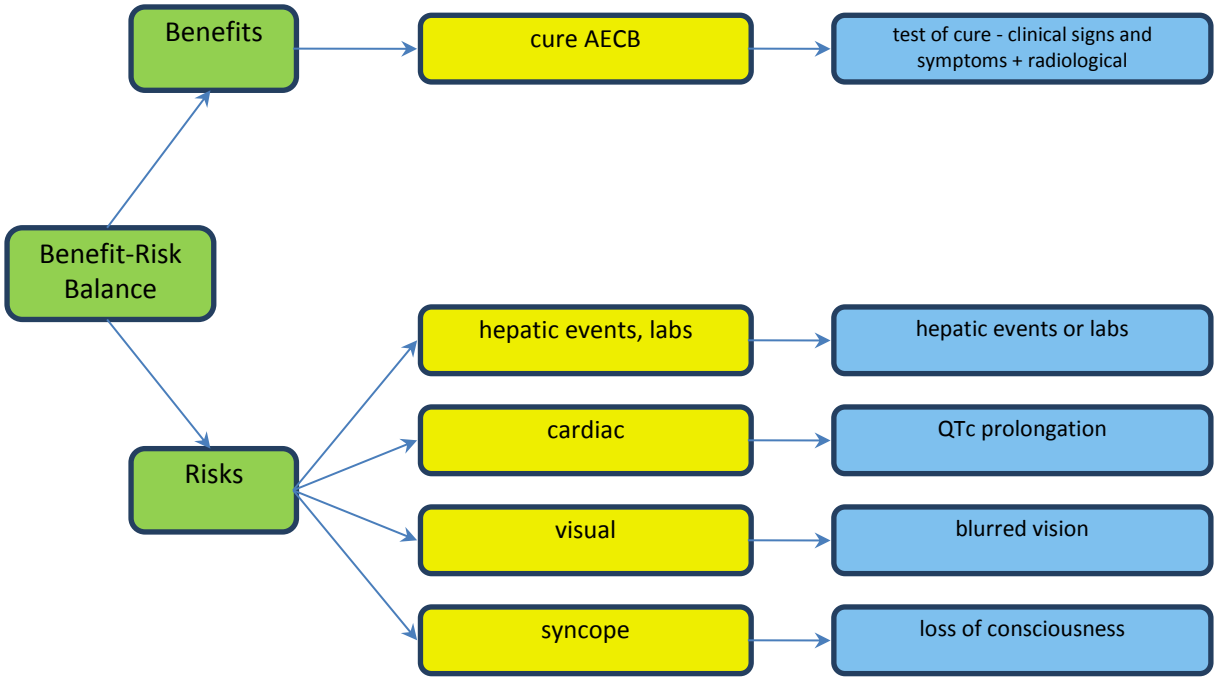
The other output that will be populated from the data table is a forest plot. It is a visualization of the risk differences (or relative risks) shown in the KBRS. Steps 5 and 6, assess outcome importance and display and interpret key B-R metrics, can be accomplished with the interpretation and display of the KBRS and forest plot.

Note that these calculations are made outside the software and the results entered into it. As described in the introduction, the BRAT Framework is intended to accommodate multiple analytical methods. The current pilot BRAT Software is designed for use with some of these methods. Although weighting is possible within the analyses that can be included in the Framework, and is part of the current example, the weighting step is conducted outside the current software tool.

4.1.2.3 Acute Exacerbation of Chronic Bronchitis (AECB)

The value tree for AECB is shown below, displaying the outcomes of interest.

Figure 4.1.2-2 value tree for AECB

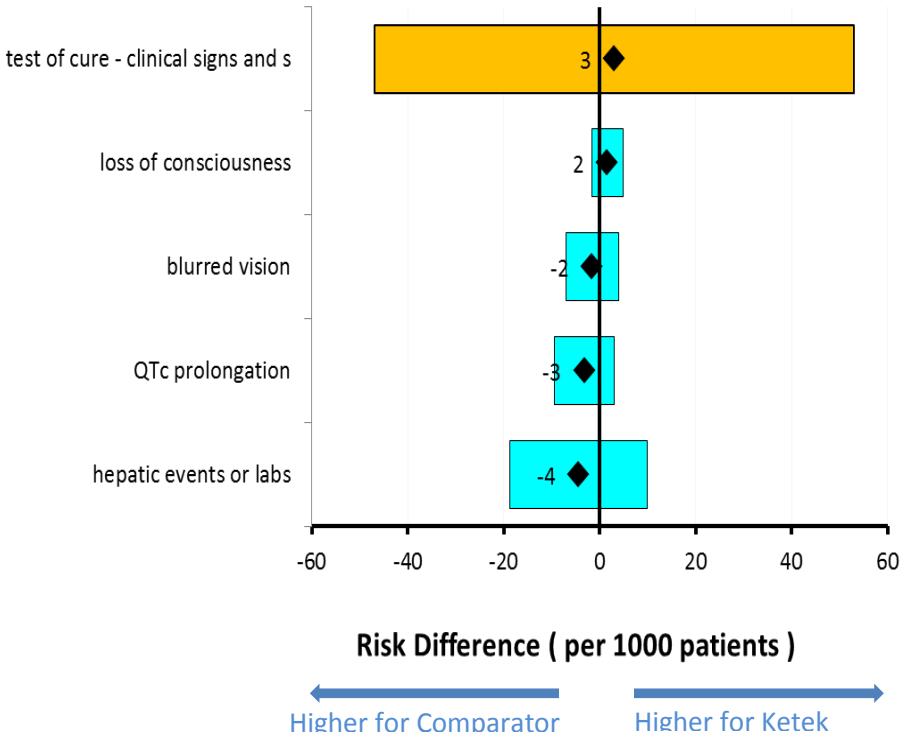


The KBRS and forest plot for AECB show the risk differences (RD) and confidence intervals for the outcomes of interest. The benefit RD was calculated in a meta-analysis. The risk data was pooled. All of the confidence intervals include 0, suggesting no benefit and no reduced risk of Ketek over the comparator in this indication.

Figure 4.1.2-3: KBRS for AECB

		Outcome	Ketek Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Ben	cure AECB	test of cure - clinical signs and	-	-	3	(-47, 53)	-	(-, -)
Risks	hepatic events, labs	hepatic events or labs	15	19	-4	(-19, 10)	-	(-, -)
	cardiac	QTc prolongation	2	5	-3	(-10, 3)	-	(-, -)
	visual	blurred vision	2	3	-2	(-7, 4)	-	(-, -)
	syncope	loss of consciousness	2	0	2	(-2, 5)	-	(-, -)

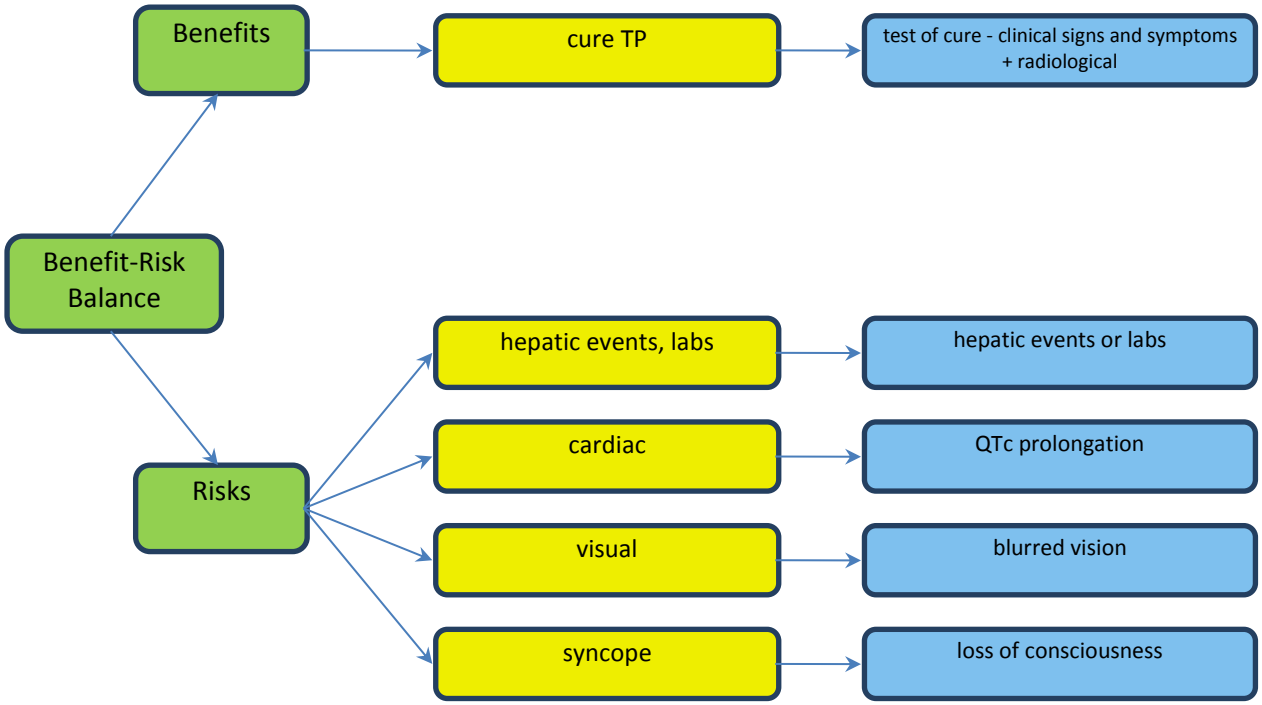
Figure 4.1.2-4: Forest plot AECB



4.1.2.4 Tonsillitis/Pharyngitis (TP)

The value tree for TP is shown below.

Figure 4.1.2-5: value tree for TP

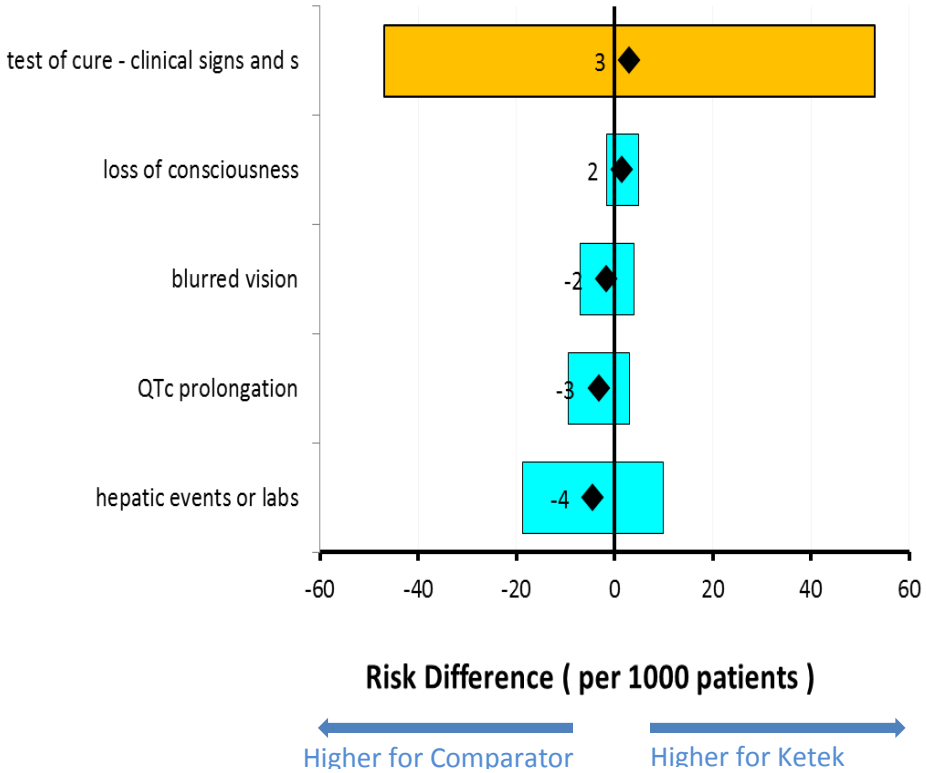


The KBRS and forest plot for TP show the risk differences (RD) and confidence intervals for the outcomes of interest. The benefit RD was calculated in a meta-analysis. The risk data was pooled. The confidence interval for the benefit includes 0, suggesting no benefit of Ketek versus the comparator. The RD for the vision risk suggests a significantly increased risk of blurred vision in patients taking Ketek versus the comparator.

Figure 4.1.2-6: KBRS for TP

		Outcome	Ketek Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Be	cure AECB	test of cure - clinical signs and	-	-	3	(-47, 53)	-	(-, -)
Risks	hepatic events, labs	hepatic events or labs	15	19	-4	(-19, 10)	-	(-, -)
	cardiac	QTc prolongation	2	5	-3	(-10, 3)	-	(-, -)
	visual	blurred vision	2	3	-2	(-7, 4)	-	(-, -)
	syncope	loss of consciousness	2	0	2	(-2, 5)	-	(-, -)

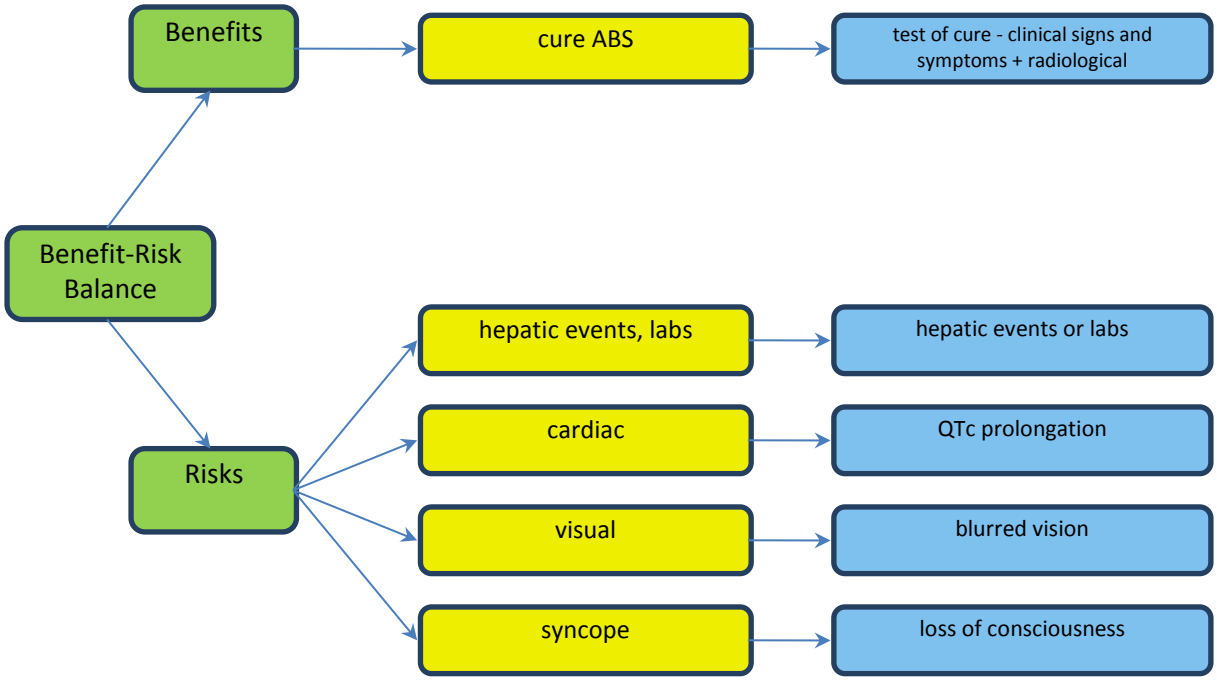
Figure 4.1.2-7: Forest plot for TP



4.1.2.5 Acute Bacterial Sinusitis (ABS)

The value tree for ABS is shown below.

Figure 4.1.2-8: Value tree for ABS

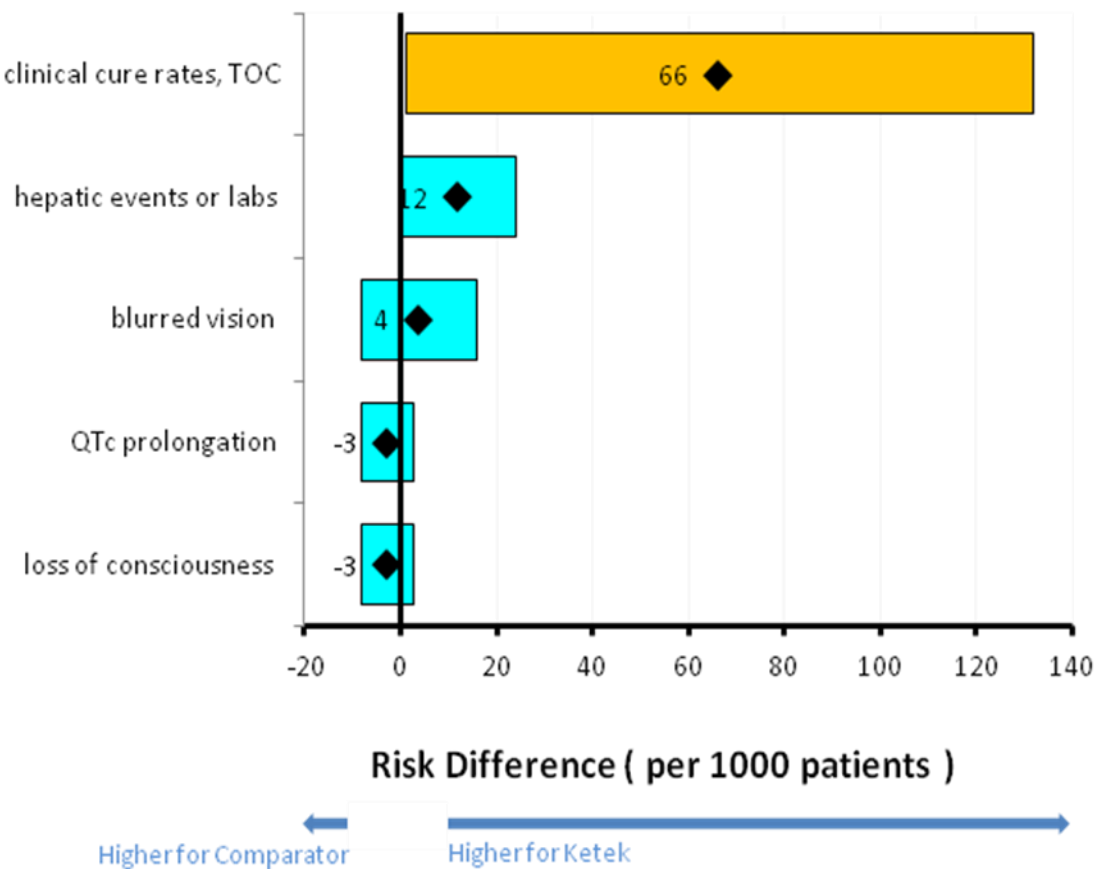


The KBRS and forest plot for ABS show the risk differences (RD) and confidence intervals for the outcomes of interest. The benefit RD was calculated in a meta-analysis. The risk data was pooled. The RD for the benefit (cure) significantly favours Ketek, but there is also a non-significant risk difference suggesting a trend in increased hepatic events or laboratory results associated with Ketek versus the comparator in this indication.

Figure 4.1.2-9: KBRS for ABS

		Outcome	Ketek Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Be	cure ABS	clinical cure rates, TOC	-	-	66	(1, 132)	-	(-, -)
Risks	hepatic events, labs	hepatic events or labs	17	5	12	(0, 24)	-	(-, -)
	cardiac	QTc prolongation	0	3	-3	(-8, 3)	-	(-, -)
	visual	blurred vision	12	8	4	(-8, 16)	-	(-, -)
	syncope	loss of consciousness	0	3	-3	(-8, 3)	-	(-, -)

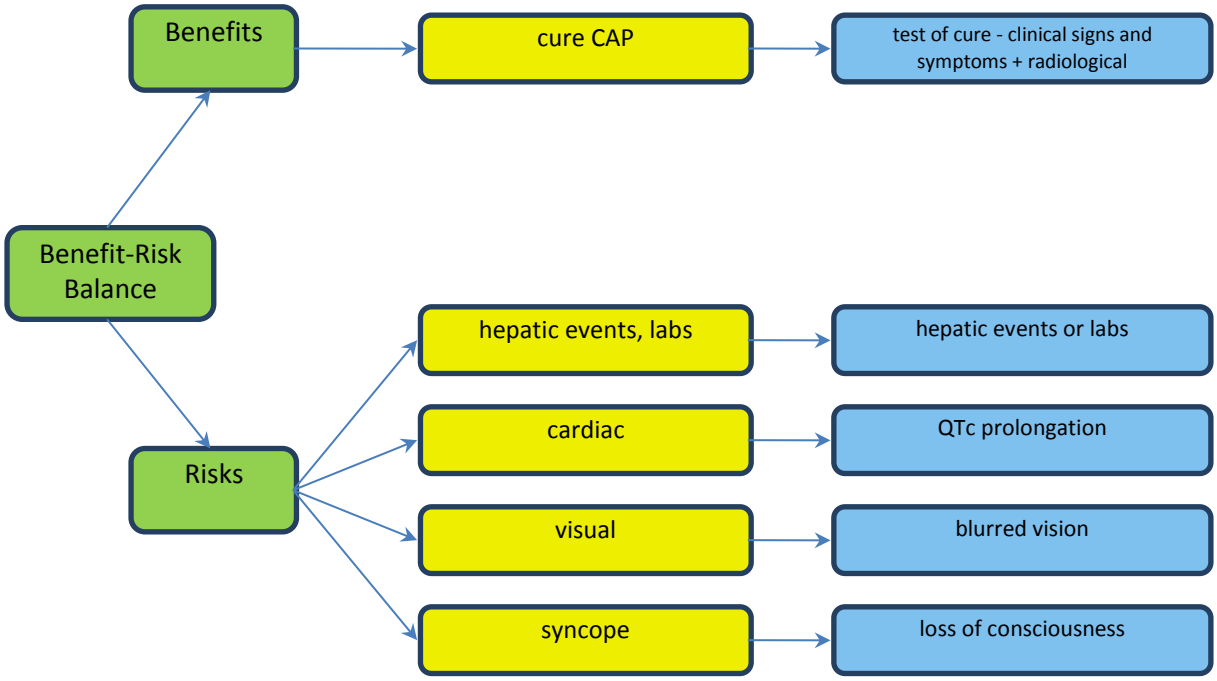
Figure 4.1.2-10: Forest plot for ABS



4.1.2.6 *Community Acquired Pneumonia (CAP)*

The value tree for CAP is shown below.

Figure 4.1.2-11: Value tree for CAP

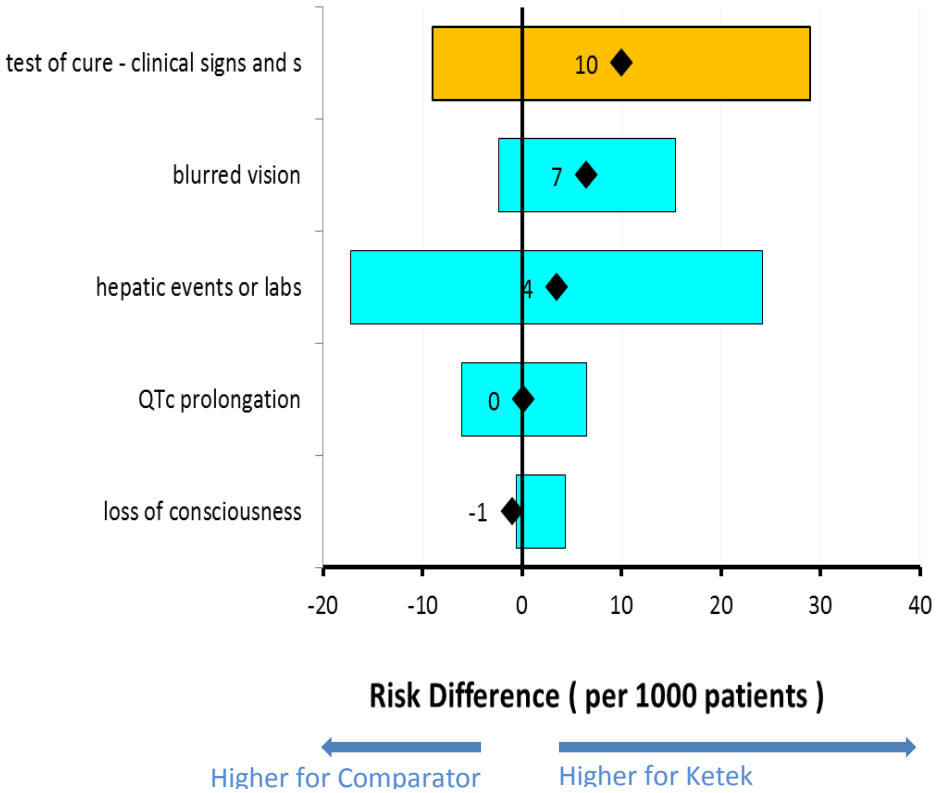


The KBRS and forest plot for CAP show the risk differences (RD) and confidence intervals for the outcomes of interest. The benefit RD was calculated in a meta-analysis. The risk data was pooled. All of the confidence intervals include 0, suggesting no significant difference between Ketek and the comparator in this indication.

Figure 4.1.2-12: KBRS for CAP

		Outcome	Ketek Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Be	cure CAP	test of cure - clinical signs and	-	-	10	(-9, 29)	-	(-, -)
Risks	hepatic events, labs	hepatic events or labs	49	46	4	(-17, 24)	-	(-, -)
	cardiac	QTc prolongation	4	4	0	(-6, 7)	-	(-, -)
	visual	blurred vision	12	6	7	(-2, 15)	-	(-, -)
	syncope	loss of consciousness	2	3	-1	(-1, 4)	-	(-, -)

Figure 4.1.2-13: Forest plot for CAP



4.1.2.7 Assessment of BRAT Framework

Overall the BRAT Framework has accomplished its purpose in displaying appropriate framing of the benefit/risk problem for each indication, and clearly displaying the risk differences for the outcomes of interest. The Framework is intended to guide users through framing and communicating their analyses. Its displays can be sorted in order of priority, but there is no weighting function, which may in part account for the differences in results between the SMAA and the BRAT. Further development of the BRAT Framework appears useful as a contribution to the benefit/risk field.

4.2 Quantitative Framework

4.2.1 Multi-Criteria Decision Analysis (MCDA)

4.2.1.1 Aims

The overall aims of this case study analysis are:

- To assess the feasibility and suitability of the approaches using Multi Criteria Decision Analysis [MCDA] model for benefit-risk assessment of drugs by the regulator, using Ketek as an example;

4.2.1.2 Data requirement and confidentiality

Data for analysis in this case study were obtained from Phrase III/IV trials on Ketek. Public data in EPAR were sought and summarized for the analysis. No issue of confidentiality was noted.

4.2.1.3 Development of MCDA model

4.2.1.3.1 Establishment of decision context

Refer to PrOACT-URL section

4.2.1.3.2 Identification of options to be appraised

This model was used to appraise Ketek compared to other comparator in 4 different indications:

- Community acquired pneumonia [CAP]
- Acute exacerbation of chronic bronchitis [AECB]
- Acute bacterial sinusitis [ABS]
- Tonsillitis and pharyngitis [TP]

4.2.1.3.3 Identification of the benefit and risk criteria and organisation in a value tree

Ketek [Telithromycin] is a semi-synthetic anti bacterial agent synthesised from erythromycin, and belongs to a new family of antibiotics – Ketolides. It was advocated as an alternative treatment when conventional beta-lactam antibiotics are contra-indicated.

The primary benefit of this analysis was cure rate compared to comparators. There were secondary benefits listed in EPAR, for example, development of antibiotics resistance microprobes. However, there were a lack of data on comparator and our group decided to concentrate only on primary benefit for the purpose of this exercise.

Compared to other macrolides, Ketek seems to be associated with a somewhat different risk profile, i.e. adverse reactions as eye disorders, which sometimes are of severe nature, and serious adverse reactions as aggravation of myasthenia gravis, loss of consciousness and acute liver failure. Apart from these side effects, prolonged QT interval on electrocardiogram is a major concern. There were little data reported in EPAR regarding absolute measurements of QT intervals in trial subjects, therefore we took a pragmatic to use incidence of syncope, which was well documented in EPAR, as a surrogate marker of clinically significant incidence of prolonged QT interval.

Benefit data of Ketek in EPAR were collected from a selection of Phrase III/IV randomised controlled studies. Data were first summarised using random effects meta-analysis. Random effect methods

were chosen to reflect the uncertainties and differences in underlying populations used in the trials. Data from different studies were pooled using method of inverse variance.

Regarding to risk, data from EPAR were already pooled between trials. We used the same method to combine risk profile between phrase III and IV studies for this model.

Benefit criteria
1] Cure rate

Risk criteria
1] Cardiac adverse events
2] Visual adverse events
3] Syncope
4] Hepatic adverse events
5] Severe adverse events
6] All adverse events

Value Tree
A total of 4 models were developed for the four indications, to accommodate changes in weightings as a different of clinical needs.

First level Criteria
Total Risks and Total Benefits of Ketek

Second level criteria
Component of benefit – difference in cure rate
Components of risk – Cardiac AE, Visual AE, Syncope, Hepatic AE, Severe AE, all adverse events.

Scoring options for each of the criteria
Ideally, the scoring options should be discussed in details with stakeholders. The range of preference score and type of criterion value function greatly affect the preference score, which will have substantial impact on final results. Our group opted for a minimalist approach, all preference scores between the two options were established on a fixed scale based on a linear preference scoring. The range of preference scale was anchored according to clinical importance based on an in-group physician opinion.

Data from EPAR suggesting that the difference in efficacies between treatment were small and we were more interested in difference in risk, margin in benefit was fixed at 0 and 100%, whereas risk were fixed at 0 and 10%.

4.2.1.3.4 Assignment of a weight to each criteria

The aim of this analysis was to examine the feasibility of using MCDA model in medicine safety decision making; however, weighting on risk and benefit is subjective and varies between regulator and end-users.

In the MCDA working framework, a decision conference between stakeholders should be held to achieve an agreed weightings and trade-offs between criteria, after reviewing preference scores.

This approach was not feasible at current work group setting, and we would address this with patient group involvement in Wave 2 studies.

For the purpose of this exercise, weighting on criteria in different indications were assigned by our in-house physician. Benefit–risk weighting were based on the clinical context. Complex weightings between risk criteria were assigned using the Measuring Attractiveness by a Categorical Based Evaluation Technique [MacBeth] approach, which was incorporated within HiView3.

4.2.1.3.5 Calculation of weighted score at each level and overall weighted score

Will be discussed in results section

4.2.1.3.6 Sensitivity analysis

Will be discussed in results section

4.2.1.4 Results

4 models were developed for this analysis based on the four indications of Ketek.

4.2.1.4.1 Community Acquired Pneumonia [CAP]

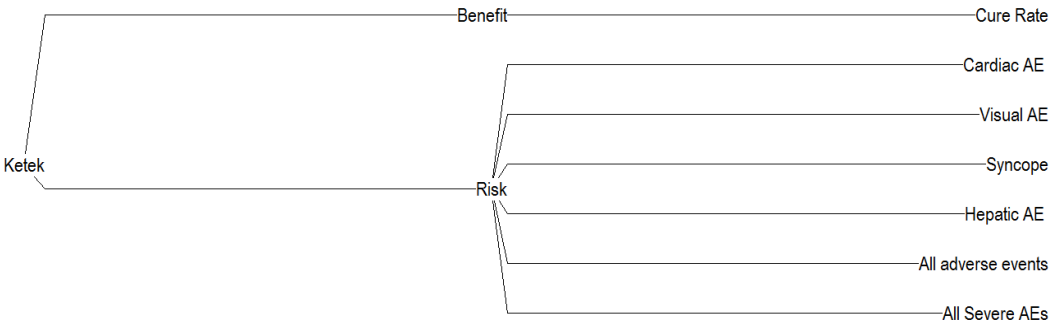


Figure 4.2.1-1: Value tree – CAP

Data and preference score

Figure 4.2.1-2: Data and preference score -CAP

Long Name	Option	Input Score	Preference Score	Weighted Score
Cure Rate	Ketek	89.5	89.50	44.75
	Comparator	89.3	89.30	44.65
Cardiac AE	Ketek	0.2	98.00	8.68
	Comparator	0.3	97.00	8.59
Visual AE	Ketek	1.2	88.00	4.62
	Comparator	0.5	95.00	4.99

Syncope	Ketek	0.0	100.00	9.24
	Comparator	0.3	97.00	8.96
Hepatic AE	Ketek	1.7	83.00	6.38
	Comparator	0.4	96.00	7.38
All adverse events	Ketek	39.3	21.40	1.98
	Comparator	37.4	25.20	2.33
All Severe AEs	Ketek	0.6	94.00	9.14
	Comparator	0.4	96.00	9.34

Weighting

Figure 4.2.1-3 below detailed weighting assigned to different criteria. There are many alternative treatments in CAP. Therefore, benefit and risk were given equal weighting. Weighting for risk sub criteria were assigned using MacBeth, based on user judgement in order of preference [Figure 4.2.1-4].

Figure 4.2.1-3: Criteria weighting - CAP

Criteria	Weight	Sub Criteria	Weight
Benefit	0.50	Cure rate	1.00
Risk	0.50	Cardiac AE	0.18
		Visual AE	0.11
		Syncope	0.18
		Hepatic AE	0.15
		Severe Adverse events	0.19
		All adverse events	0.18

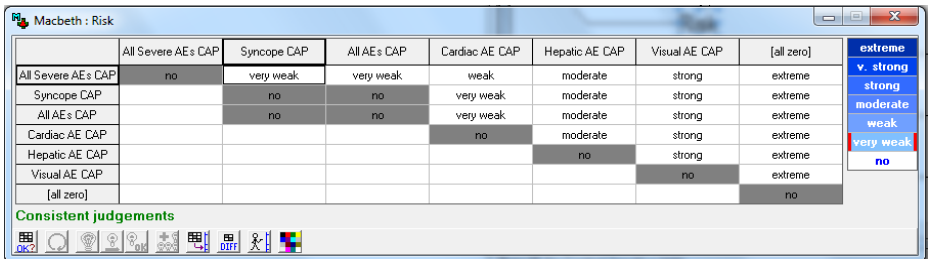


Figure 4.2.1-4: MacBeth approach on risk criteria: CAP

Model results

Overall results showed comparator was a more preferable choice by a small margin. The small difference in cure rate with Ketek [Figure 4.2.1-5] was outweighed by difference in risk in adverse events [Figure 4.2.1-6].

Although there was a concern with prolonged QT intervals with Ketek, there were lower incidence of syncope in this group and resulted a higher weighted score with Ketek scored along with cure rate. Compared to comparators, Ketek achieved a lower score in risk of hepatic, visual and overall adverse events [Figure 4.2.1-7].

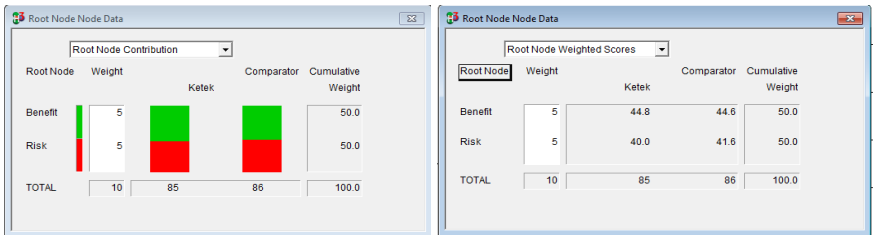


Figure 4.2.1-5: Overall results: CAP

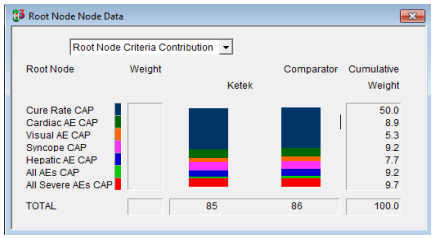


Figure 4.2.1-6: Contribution of risk criteria: CAP

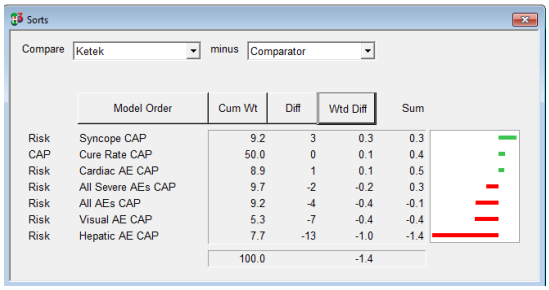
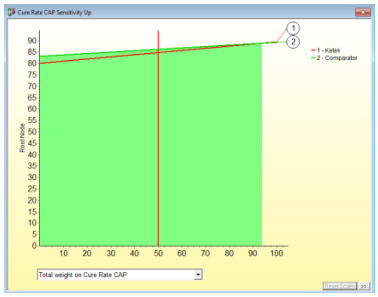


Figure 4.2.1-7: Weighted difference between Ketek and Comparator: CAP

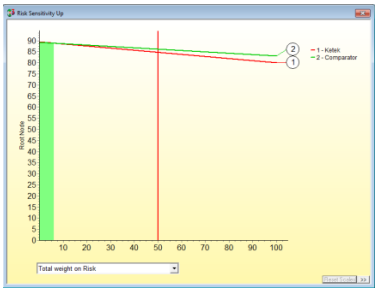
Sensitivity testing

Sensitivity analysis suggests the result from this model was not easily influenced by the weightings assigned. The result would only change in preference to Ketek if there was a large increase in

weighting over cure rate [Figure 4.2.1-8], syncope or cardiac adverse events [Figure 4.2.1-9]. Changes in weighting on visual, hepatic AE, any AE or any severe AE would not affect the final result [Figure 4.2.1-9].

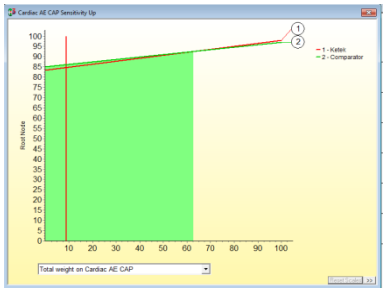


[A] Benefit

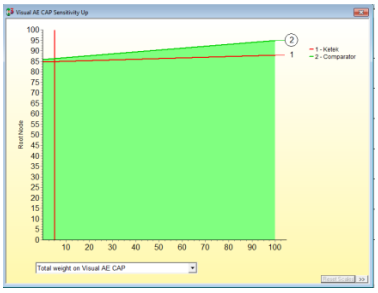


[B] Risk

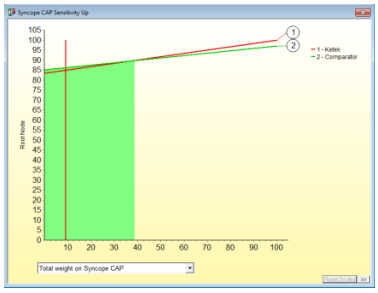
Figure 4.2.1-8: Sensitivity testing - Benefit/Risk: CAP



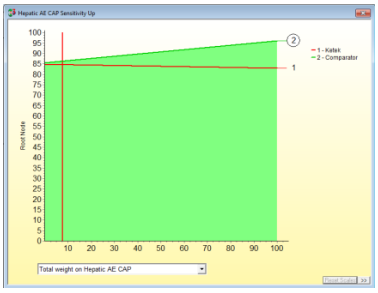
[A] Cardiac AE



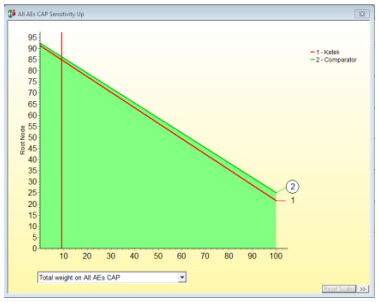
[B] Visual AE



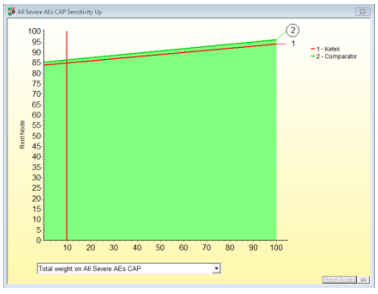
[C] Syncope



[D] Hepatic AE



[E] All adverse AE



[F] All severe AE

Figure 4.2.1-9: Sensitivity testing - Risk criteria: CAP

4.2.1.4.2 Acute exacerbation of chronic bronchitis [AECB]

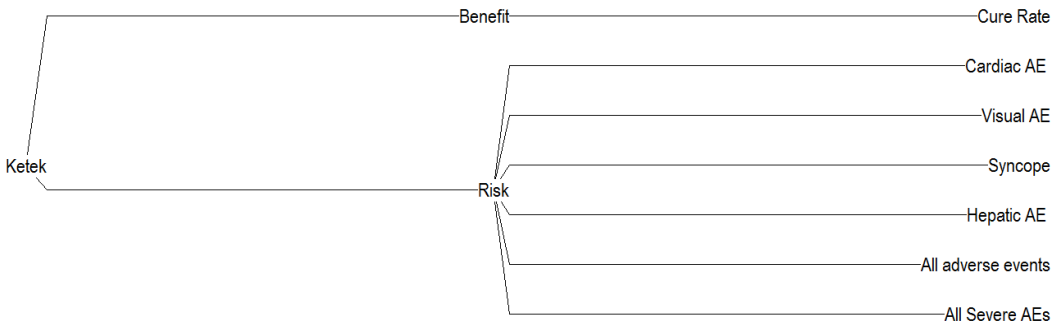


Figure 4.2.1-10: Value tree – AECB

Data and preference score

Figure 4.2.1-11: Data and preference score -AECB

Long Name	Option	Input Score	Preference Score	Weighted Score
Cure Rate	Ketek	86.1	86.1	60.27
	Comparator	84.9	84.9	59.43
Cardiac AE	Ketek	1.5	85	5
	Comparator	1.9	81	4.76
Visual AE	Ketek	0.2	98	3.18
	Comparator	0.1	99	3.21
Syncope	Ketek	0.2	98	4.68
	Comparator	0.5	95	4.54
Hepatic AE	Ketek	0.2	98	4.68
	Comparator	0	100	4.78
All adverse events	Ketek	27.9	44.2	2.3
	Comparator	29.8	40.4	2.1
All Severe AEs	Ketek	1.9	81	4.96
	Comparator	1.8	82	5.02

Weighting

Figure 4.2.1-12 below detailed weighting assigned to different criteria. There were concerns with an existing antibiotics resistance in AECB. Therefore, benefit was given a higher weighting. Weighting for risk sub criteria were assigned using MacBeth, based on user judgement in order of preference.

Figure 4.2.1-12 Criteria weighting - AECB

Criteria	Weight	Sub Criteria	Weight
Benefit	0.70	Cure rate	1.00
Risk	0.30	Cardiac AE	0.16
		Visual AE	0.11
		Syncope	0.16
		Hepatic AE	0.20
		Severe Adverse events	0.20
		All adverse events	0.17

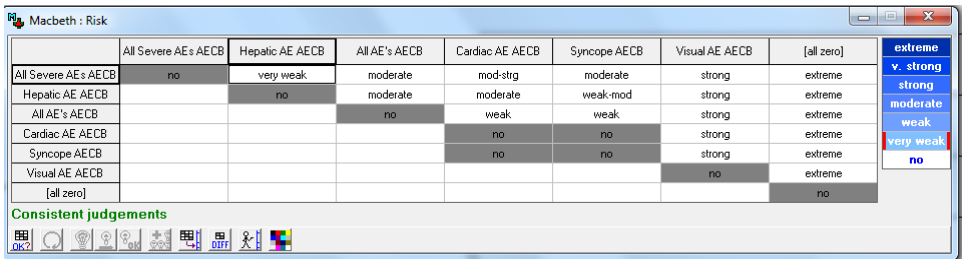


Figure 4.2.1-13 MacBeth approach on risk criteria: AECB

Model results

Overall results showed Ketek would be a more preferable choice by a small margin. There was a small difference in cure rate with Ketek [Figure 4.2.1-14] as well as lower combined score in adverse events [Figure 4.2.1-15].

Ketek achieved a higher weighted score with cure rate, incidence of cardiac and hepatic AE, as well as overall adverse event rate. [Figure 4.2.1-16].

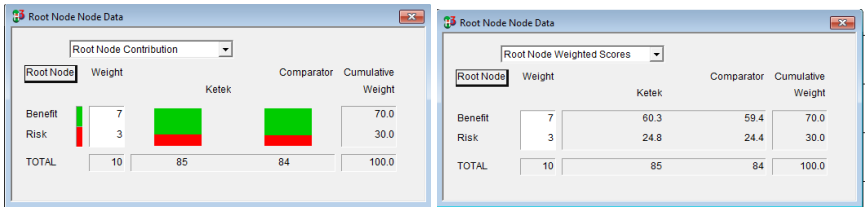


Figure 4.2.1-14: Overall results: AECB

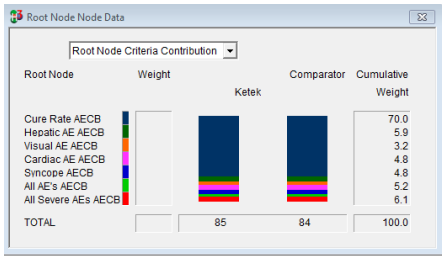


Figure 4.2.1-15: Contribution of risk criteria: AECB

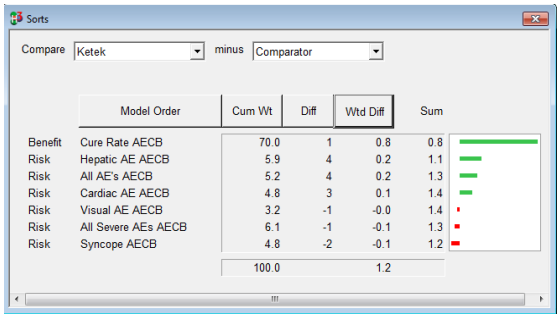
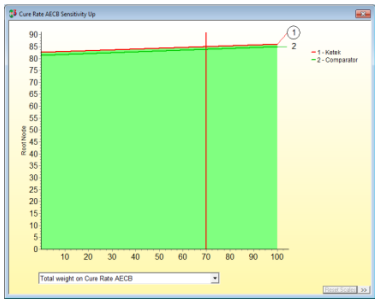


Figure 4.2.1-16: Weighted difference between Ketek and Comparator: AECB

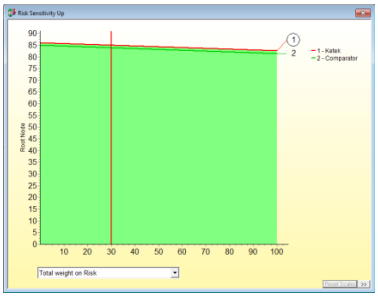
Sensitivity testing

Sensitivity testing suggesting the result from this model was not easily influenced by weightings assigned.

The result suggested this model will need a large increase in weighting over visual AE, syncope or all severe events to change the result [Figure 4.2.1-18]. Changing in weighting on overall risk or benefit would not affect final results [Figure 4.2.1-17].

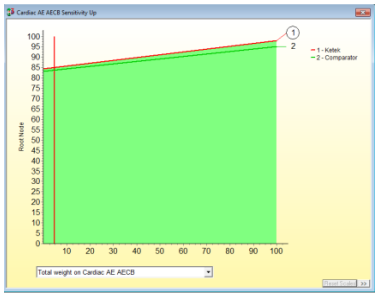


[A] Benefit

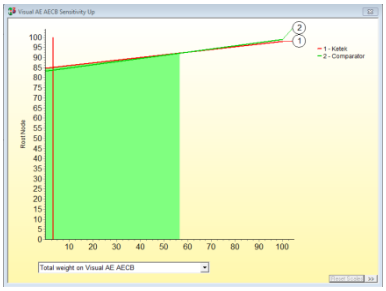


[B] Risk

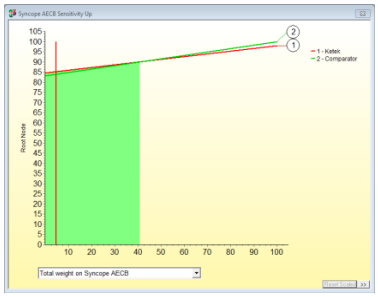
Figure 4.2.1-17: Sensitivity testing - Benefit/Risk: AECB



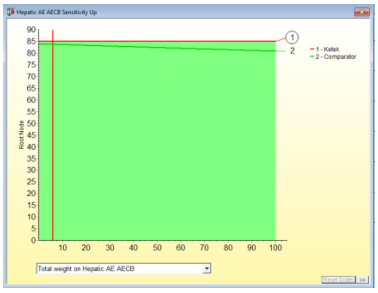
[A] Cardiac AE



[B] Visual AE

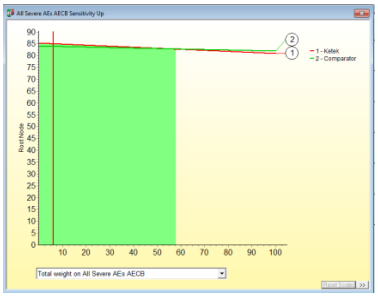


[C] Syncope



[D] Hepatic AE

[E] All adverse AE



[F] All severe AE

Figure 4.2.1-18: Sensitivity testing - Risk criteria: AECB

4.2.1.4.3 Acute bacterial sinusitis [ABS]

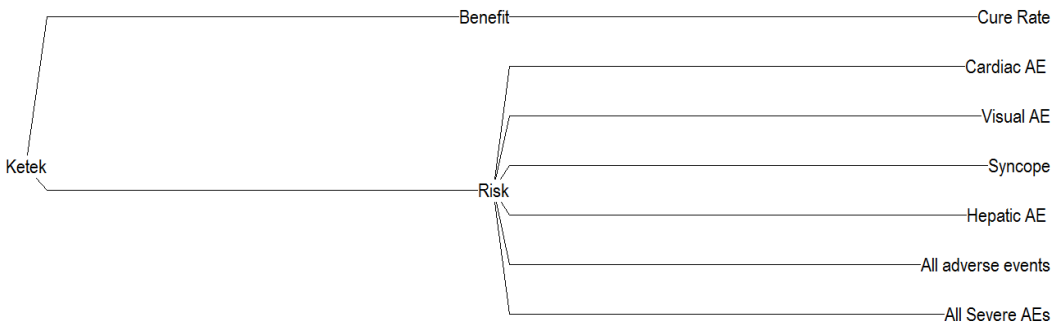


Figure 4.2.1-19: Value tree – ABS

Data and preference score

Figure 4.2.1-20: Data and preference score -ABS

Long Name	Option	Input Score	Preference Score	Weighted Score
Cure Rate	Ketek	77.9	77.9	38.95
	Comparator	77	77	38.5
Cardiac AE	Ketek	3.9	61	4.72
	Comparator	3.9	61	4.72
Visual AE	Ketek	1	90	4.61
	Comparator	0.6	94	4.82
Syncope	Ketek	0.2	98	9.48
	Comparator	0.3	97	9.38
Hepatic AE	Ketek	2.54	74.6	6.93
	Comparator	1.33	86.7	8.05
All adverse events	Ketek	0.5	95	8.09
	Comparator	0.3	97	8.26
All Severe AEs	Ketek	5.2	48	4.64
	Comparator	6.8	32	3.09

Weighting

Figure 4.2.1-21 below detailed weighting assigned to different criteria. After considering the clinical implications and availability of alternative treatments, risk and benefit were given equal weight. Weighting for risk sub criteria were assigned using MacBeth, based on user judgement in order of preference [Figure 4.2.1-22].

Figure 4.2.1-21: Criteria weighting - ABS

Criteria	Weight	Sub Criteria	Weight
Benefit	0.50	Cure rate	1.00
Risk	0.50	Cardiac AE	0.17
		Visual AE	0.10
		Syncope	0.19
		Hepatic AE	0.15
		Severe Adverse events	0.19

		All adverse events	0.19

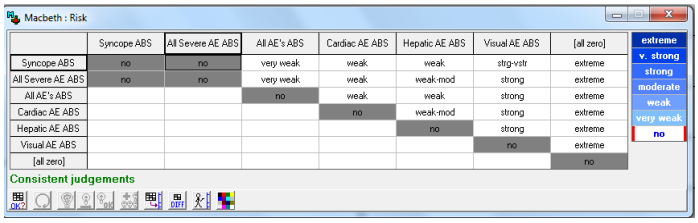


Figure 4.2.1-22: MacBeth approach on risk criteria: ABS

Model results

Overall results showed Ketek was a more preferable choice by a tiny margin. Both comparator and Ketek achieved almost equivalent score in benefit and risks. [Figure 4.2.1-23, Figure 4.2.1-24]

Ketek achieved a higher weighted score with cure rate and severe AE, as well as risk of syncope [Figure 4.2.1-25], whereas Ketek scored much lower in case of all adverse events.

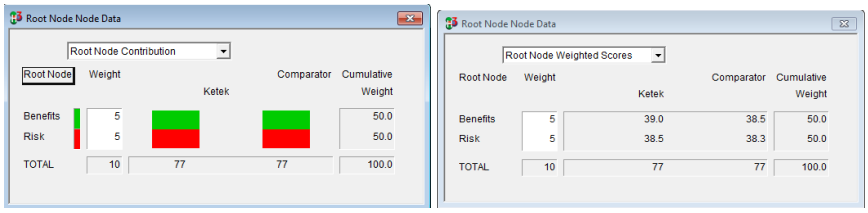


Figure 4.2.1-23: Overall results: ABS

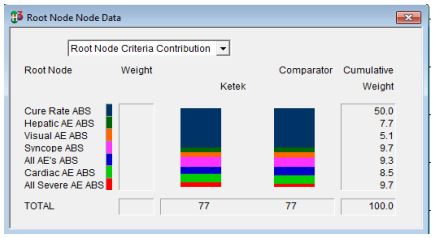


Figure 4.2.1-24: Contribution of risk criteria: ABS

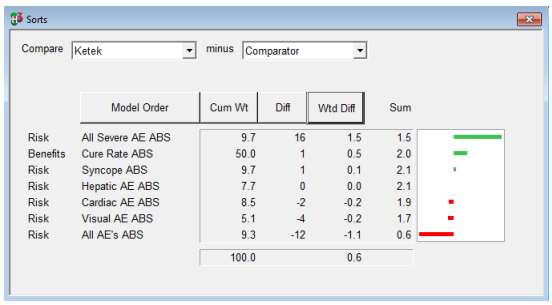
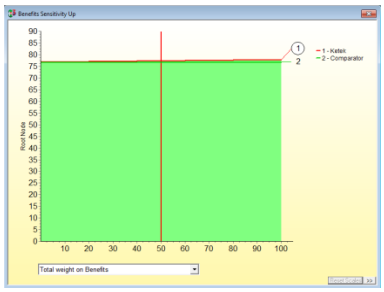


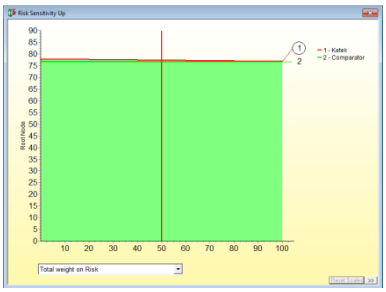
Figure 4.2.1-25: Weighted difference between Ketek and Comparator: ABS

Sensitivity testing

Sensitivity testing suggesting the result from this model could be influenced by small changes in weightings assigned. An increase in weighting in total adverse events or reduce weighting in overall severe adverse events would flavour comparator [Figure 4.2.1-27]. Changing in weighting on overall risk or benefit would not affect final results [Figure 4.2.1-26].

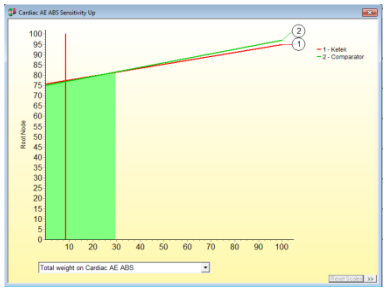


[A] Benefit

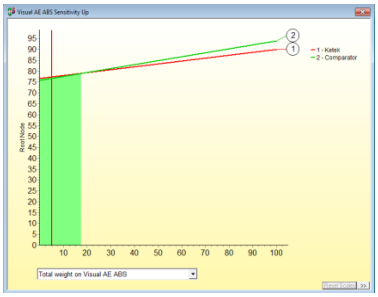


[B] Risk

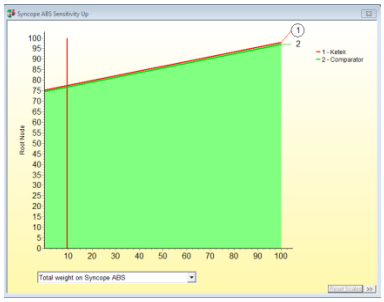
Figure 4.2.1-26: Sensitivity testing - Benefit/Risk: ABS



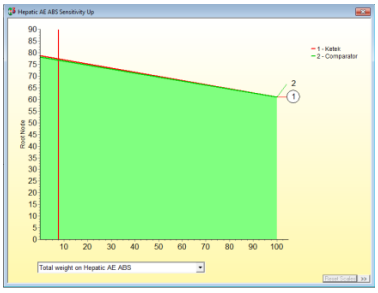
[A] Cardiac AE



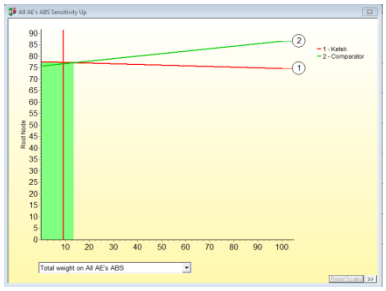
[B] Visual AE



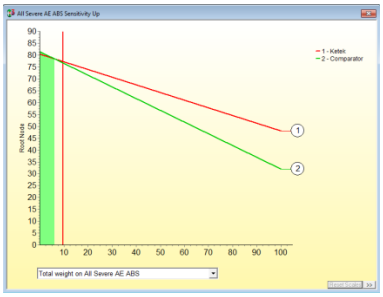
[C] Syncope



[D] Hepatic AE



[E] All adverse AE



[F] All severe AE

Figure 4.2.1-27: Sensitivity testing - Risk criteria: ABS

4.2.1.4.4 Tonsillitis and pharyngitis [TP]

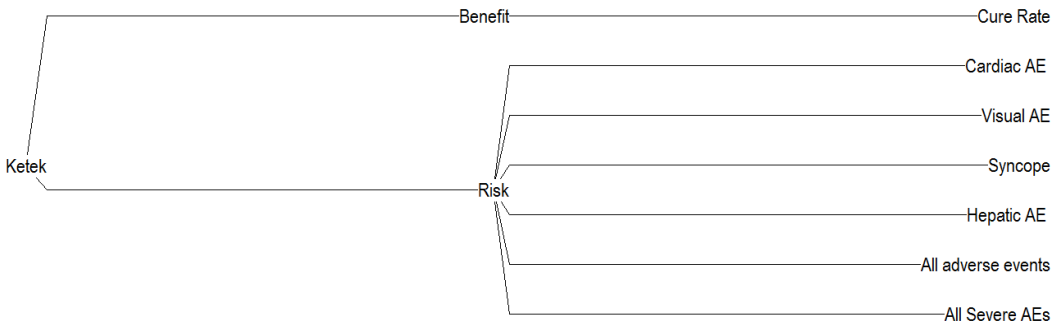


Figure 4.2.1-28: Value tree – TP

Data and preference score

Figure 4.2.1-29 Data and preference score -TP

Long Name	Option	Input Score	Preference Score	Weighted Score
Cure Rate	Ketek	87.9	87.9	26.37
	Comparator	88.6	88.6	26.58
Cardiac AE	Ketek	0	100	11.3
	Comparator	0	100	11.3
Visual AE	Ketek	2.1	79	6.07
	Comparator	0	100	7.68
Syncope	Ketek	0	100	10.29
	Comparator	0	100	10.29
Hepatic AE	Ketek	52.5	12.5	1.74
	Comparator	47.2	21.33	2.97
All adverse events	Ketek	1.6	84	10.35
	Comparator	2.8	72	8.87
All Severe AEs	Ketek	1.2	88	12.75
	Comparator	1.2	88	12.75

Weighting

Figure 4.2.1-29 below detailed weighting assigned to different criteria. After considering the clinical implications and availability of alternative treatments, risks were given higher weight compared to benefit. Weighting for risk sub criteria were assigned using MacBeth, based on user judgement in order of preference (Figure 4.2.1-31)

Figure 4.2.1-30: Criteria weighting - TP

Criteria	Weight	Sub Criteria	Weight
Benefit	0.30	Cure rate	1.00
Risk	0.70	Cardiac AE	0.16
		Visual AE	0.11
		Syncope	0.15
		Hepatic AE	0.18
		Severe Adverse events	0.21
		All adverse events	0.20

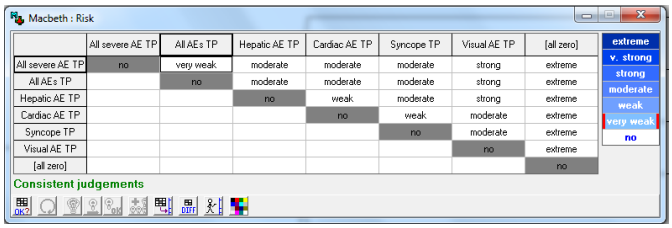


Figure 4.2.1-31: MacBeth approach on risk criteria: TP

Model results

Overall results showed comparator was a more preferable choice by a small margin. Both comparator and Ketek achieved almost equivalent score in benefit and risks. [Figure 4.2.1-33, Figure 4.2.1-34]

Ketek achieved a higher weighted score with lower hepatic; however, scored lower with cure rate, visual and all adverse events [Figure 4.2.1-34].

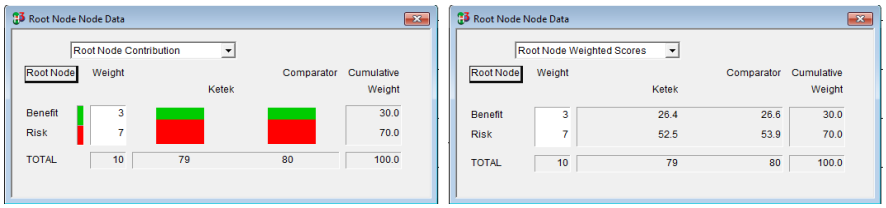


Figure 4.2.1-32: Overall results: TP

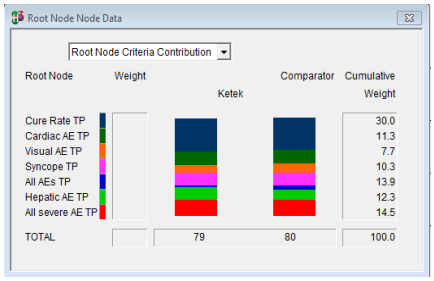


Figure 4.2.1-33: Contribution of risk criteria: TP

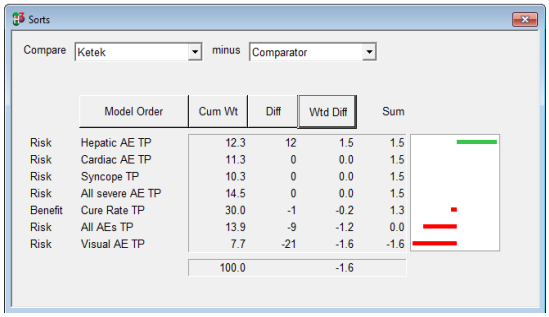
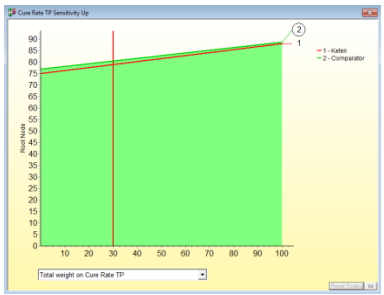


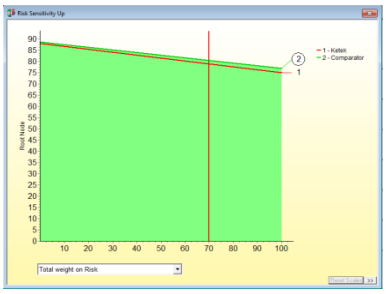
Figure 4.2.1-34: Weighted difference between Ketek and Comparator: TP

Sensitivity testing

Sensitivity testing suggesting the result from this model could be influenced by changes in weightings assigned to visual and hepatic AE. An increase in weighting in hepatic AE or a decrease in weighting in visual AE would flavour Ketek [Figure 4.2.1-36]. Changing in weighting on overall risk or benefit would not affect final results [Figure 4.2.1-35].

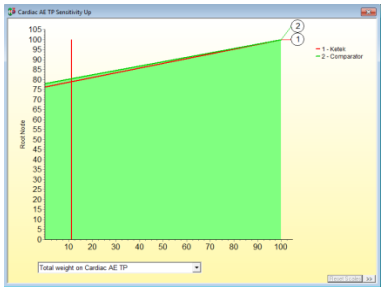


[A] Benefit

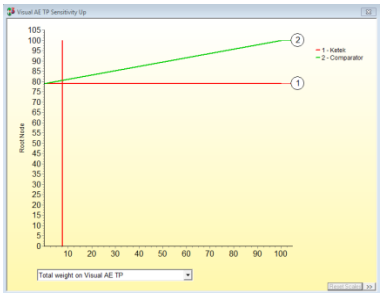


[B] Risk

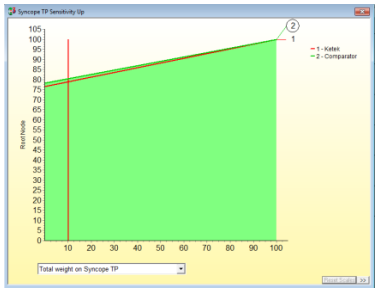
Figure 4.2.1-35: Sensitivity testing - Benefit/Risk: TP



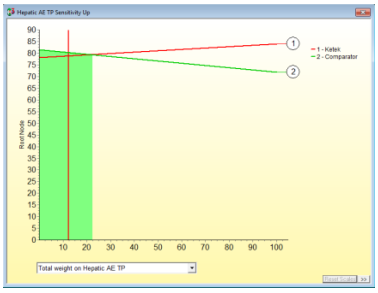
[A] Cardiac AE



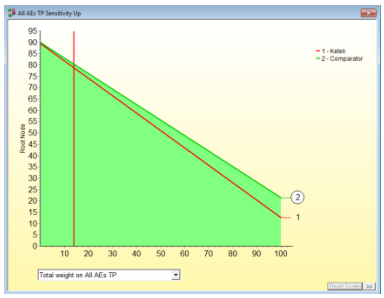
[B] Visual AE



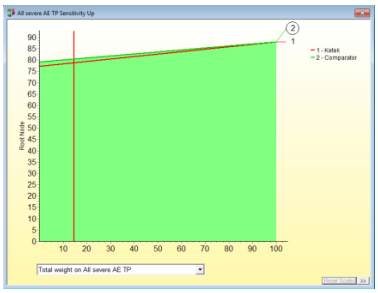
[C] Syncope



[D] Hepatic AE



[E] All adverse AE



[F] All severe AE

Figure 4.2.1-36: Sensitivity testing - Risk criteria: TP

4.2.1.5 Summary

The MCDA model suggest that Ketek was more preferable compared to comparator in case of AECB and ABS; less preferable in CAP and TP, although by small margin in all cases. The results from ABS and TP models were sensitive to changes in weighting assigned. The purpose of this exercise was to examine the feasibility of the technique. Albeit data used in the model are realistic, criteria weightings used in these models were fictitious. The final results of MCDA models are inevitably affected by the weighting assigned; therefore the current results should not be taken earnestly.

4.2.2 Stochastic Multi-criteria Acceptability Analysis (SMAA)

4.2.2.1 Context of the study

Ketek was approved for indication AECB (acute exacerbation of chronic bronchitis), TP (Tonsillitis/Pharyngitis), ABS (Acute bacterial sinusitis) and CAP (Community-Acquired Pneumonia) in July 2001 by EMA. In Feb 2007, FDA authorised a new Ketek labelling with removal of the indications ABS and AECB from the labelling. This exercise is to revisit this decision by comparing Ketek with its comparators using Phase III and IV clinical trials (in EPAR summary) as source data. This exercise is supposed to be in the suit of regulatory agents. The preferences used in this analysis however are not genuine from a survey of regulatory perspectives, they are mock preferences for the purpose of applicability and acceptability checks of the methodology.

4.2.2.2 SMAA (Stochastic Multi-criteria Acceptability Analysis), the rational

In brief, SMAA is a generalization of MCDA to include uncertainty into decision analysis. In SMAA, the performance of an alternative on a criterion is a distribution rather than a single value as that in MCDA (the mean, usually). The choices of weights across criteria, in addition to fixed values of choices, can be in a range or follow some distributions. As a consequence, the balance of benefits and risks for an alternative is also a distribution. SMAA uses the probability that an alternative has the largest balance among all alternative as evidence for alternative selection. The realization of SMAA is through simulation means. An program needs to run MCDA with sample performances and weights drawn from the corresponding distributions and repeat this procedure many times (1000000, say) to summarize the results of different runs. The existing software is jsmaa, which currently deals with linear utility only.

4.2.2.3 Analysis by indication

In this case study, the distribution of each alternative on each criterion is derived with a Bayesian approach. Details are stated below.

4.2.2.3.1 AECB

Decision context

This exercise is to make decision by comparing Ketek with its comparators, amoxicillin-clavulanic acid, cefuroxime, and clarithromycin on AECB indication with Phase III and IV clinical trial data. The comparison however cannot be made to all comparators by taking each comparator as an alternative since the risk data available for this analysis are pooled over all comparators. Therefore, the combined performances of all comparators are taken as the performance of a single alternative

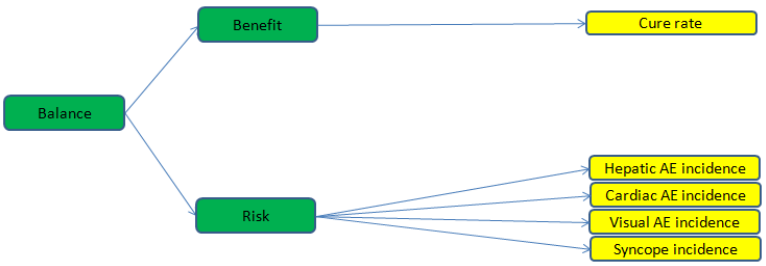
which we still name as 'Comparator'. The decision context is then about the selection between 'Ketek' and 'Comparator' for AECB.

Alternatives
Ketek; Comparator

Criteria
Benefit: Cure rate

Risks: Hepatic AE , Cardiac AE, Visual, and Syncope

The value tree from the benefit and risk criteria is shown below:



Source of data

EPAR
1. Cure rates of Ketek and its comparators were extracted from three phase III clinical trials
2. Incidences of cardiac AE, hepatic AE, visual AE, syncope pooled from phase III and VI clinical trials of Ketek and its comparator.

Analysis and results
Criteria evaluation for each alternative: In this analysis, a Bayesian approached is adopted to derive the distributions for all alternatives on all criteria. For AECB cure rate, from non-informative prior Beta(1,1), the distribution of cure rate is updated from observed rates in three phase III clinical studies. The distribution of incidence of AE of each body system is updated from non-informative prior Beta(1,1) with pooled data. The resulting posterior distributions of all criteria for Ketek and its comparator are listed as the following.

Figure 4.2.2-1: Distributions of Ketek and its comparator on all criteria

Alternative
Name: Ketek_AECB
Measurements

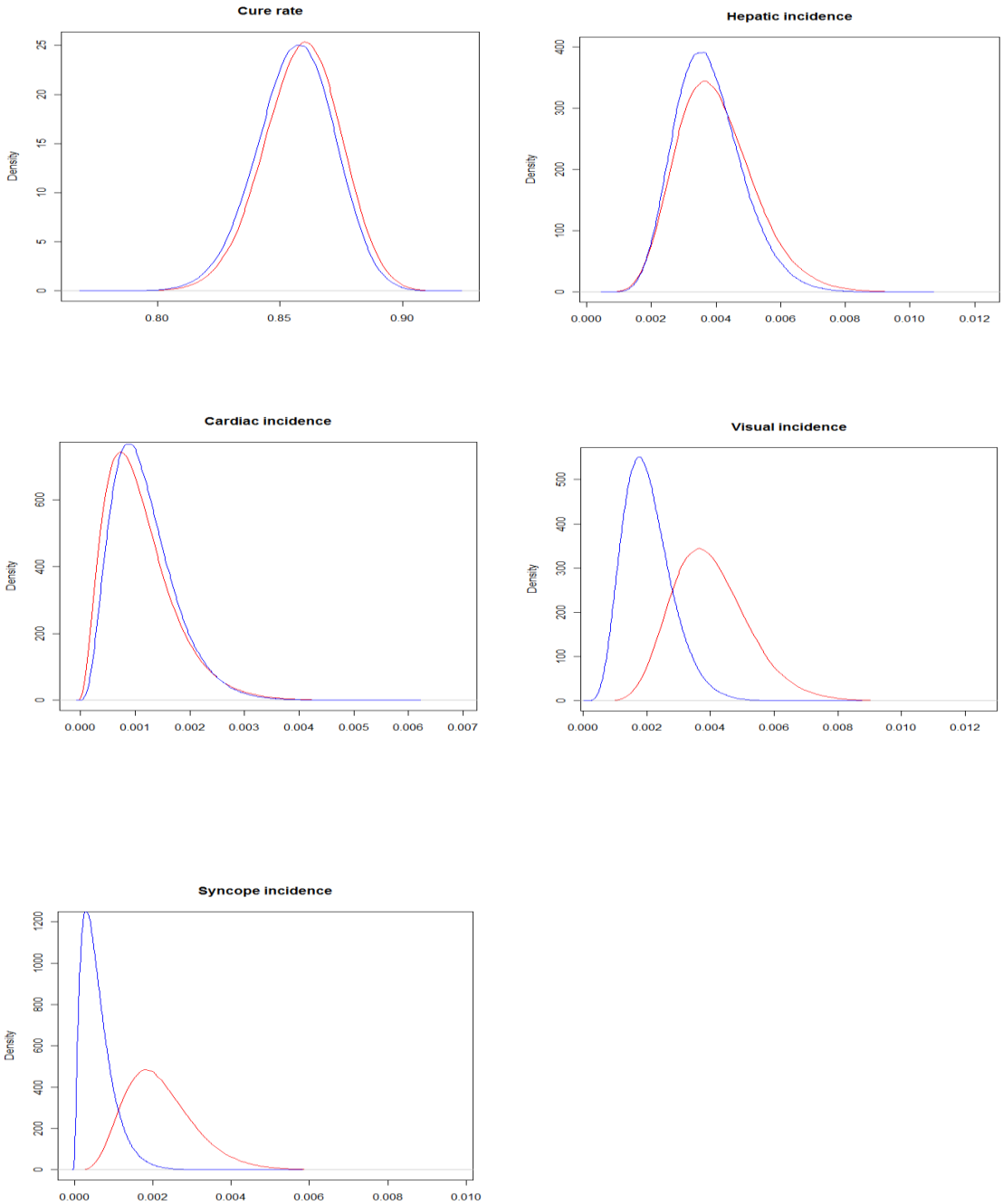
Criterion	Measurement								
hepatic AE	Beta	α	11.0	β	2732.0	min	0.0	max	1.0
cardiac AE	Beta	α	3.0	β	2740.0	min	0.0	max	1.0
visual AE	Beta	α	11.0	β	2732.0	min	0.0	max	1.0
syncope	Beta	α	6.0	β	2737.0	min	0.0	max	1.0
cure rate	Beta	α	414.0	β	68.0	min	0.0	max	1.0

Alternative
Name: comparator
Measurements

Criterion	Measurement								
hepatic AE	Beta	α	13.0	β	3417.0	min	0.0	max	1.0
cardiac AE	Beta	α	4.0	β	3426.0	min	0.0	max	1.0
visual AE	Beta	α	7.0	β	3423.0	min	0.0	max	1.0
syncope	Beta	α	2.0	β	3428.0	min	0.0	max	1.0
cure rate	Beta	α	417.0	β	70.0	min	0.0	max	1.0

Graphical representations of these distributions are given below.

Figure 4.2.2-2: Distributions of Ketek (red) and its comparator (blue) on all criteria

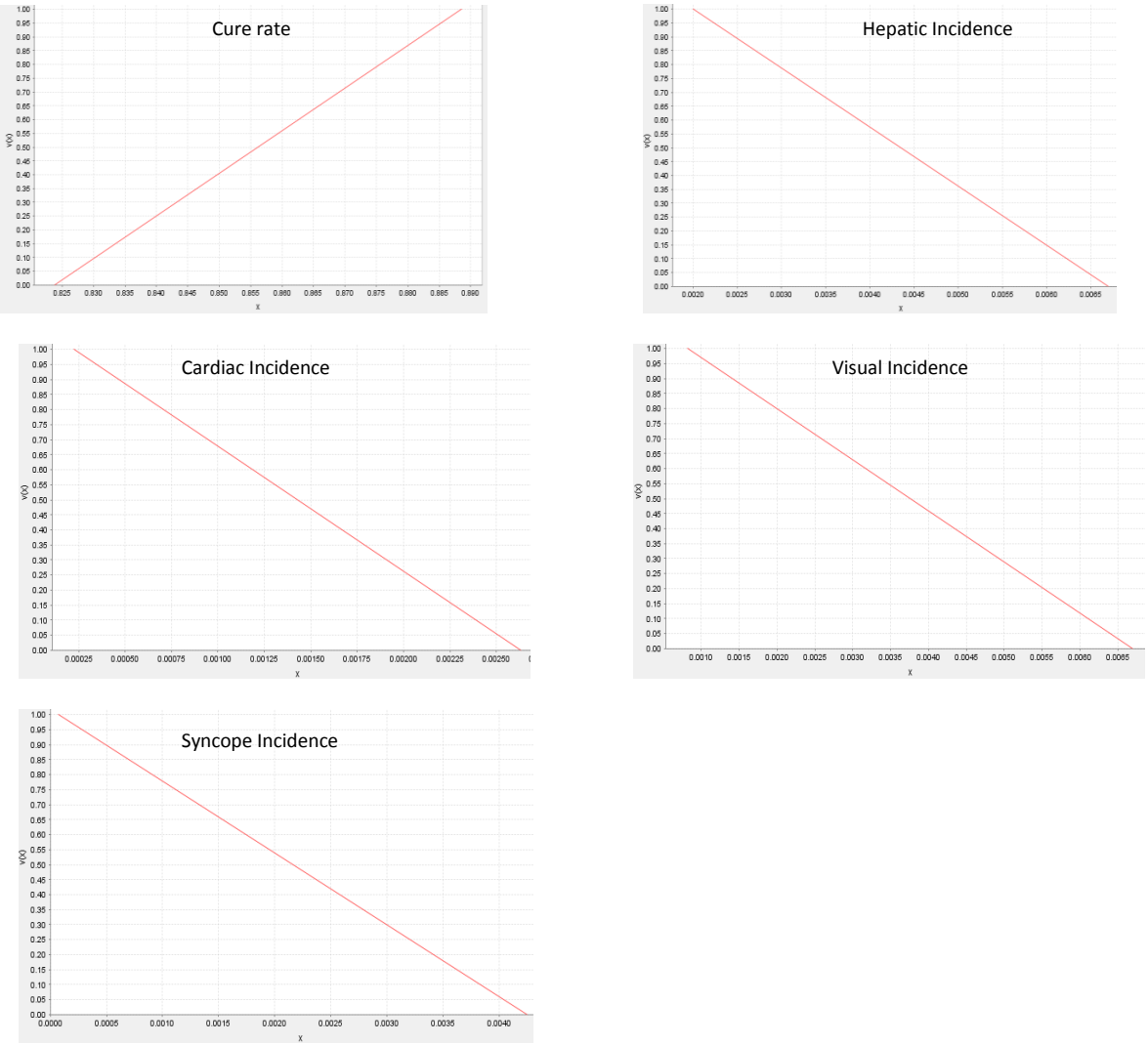


Utility

Utility of each criterion is a monotone function taking value in range [0,1] with 0 for the least preferred value and 1 for the most preferred value. Outside the most preferred and least preferred, the utility keeps as 1 and 0.

In this analysis we use linear utility function. The least preferred value and most preferred value of the benefit criterion are the lower end and upper end of 95%CI for both alternatives. The least preferred value and most preferred value of each risk criterion are the upper end and lower end of 95%CI for both alternatives. The shape of utility function for each criterion is presented below

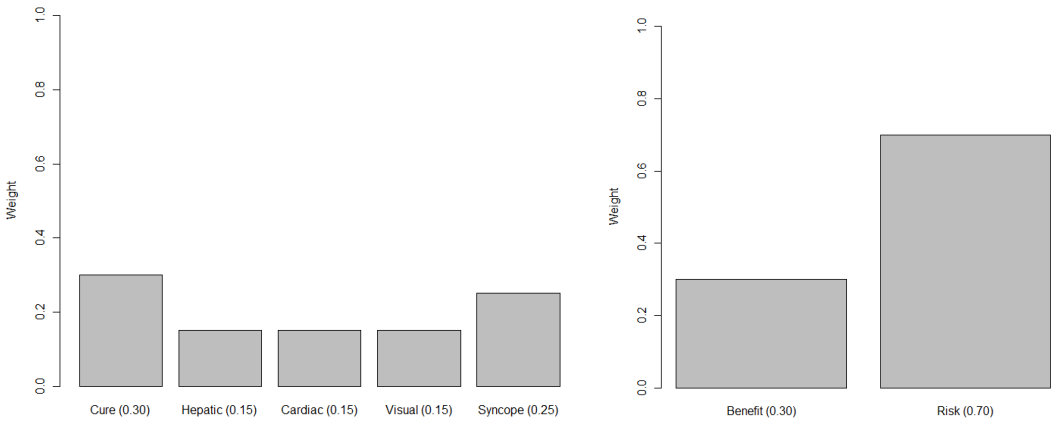
Figure 4.2.2-3: Utility function by criteria



Value function and choice of weights

The value function, which represents the balance of benefit and risk, is weighted sum of utilities over all criteria. The choice of weights in this analysis is shown below

Figure 4.2.2-4: Weights cross the five criteria and benefit, risk total



Ranking the options

In SMAA, the so-called rank acceptability index for an alternative is the probability that this alternative has the largest value function among all alternatives. The rank acceptability index of Ketek and its comparator is calculated through simulation means from the posterior distributions of the criteria using jsmaa software. The simulation goes through the following steps:

From posterior distribution of each alternative on each criterion, a random sample is drawn. Each alternative thus has sampled values on all criteria.

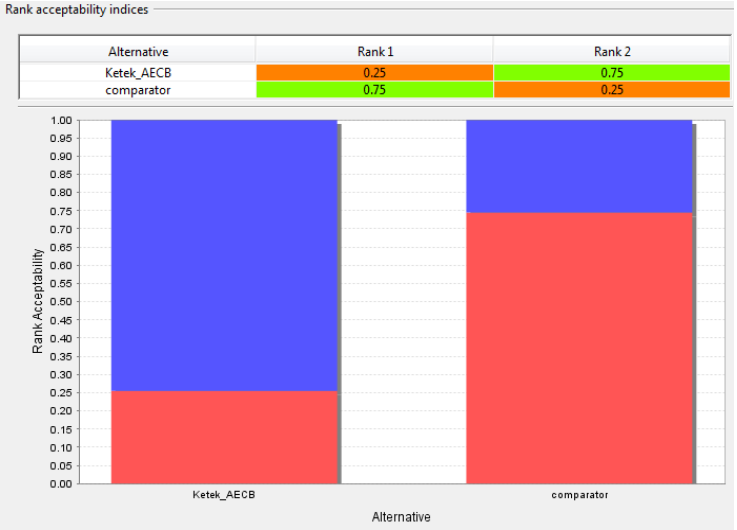
The value function for each alternative is calculated from the samples in Step 1 (converts them into utility and then calculates the weighted sum of utility). The alternative with larger value function is recorded as winner.

Repeat Step 1 and Step 2 n times (1000000, say) and calculate the number of times each alternative is winner.

Rank acceptability index for each alternative is calculated by the number of times (the alternative is winner) divided by total run number n.

The resulting rank acceptability index is shown below.

Figure 4.2.2-5: Rank acceptability of Ketek and its comparator



The conclusion is then: Ketek is worse than its comparator.

Sensitivity analysis by means of missing weights

Missing weights

We choose missing weights for a sensitivity analysis. Missing weight means any weight assignment to the five criteria is equally likely. In the terminology of probability, this means weight vector is uniformly distributed in the weight space (a simplex in 5 dimensional Euclid space).

Ranking the options under missing weights

Under the missing weigh setting, the rank acceptability index of Ketek and its comparator is calculated through simulation means from the posterior distributions of the criteria and uniform distribution of weights. The procedure is

Draw a random sample from posterior distribution of each alternative on each criterion. Each alternative then has sampled values on all criteria. Draw a random sample of weight vector from uniform distribution on weight space (5 components sum up to 1).

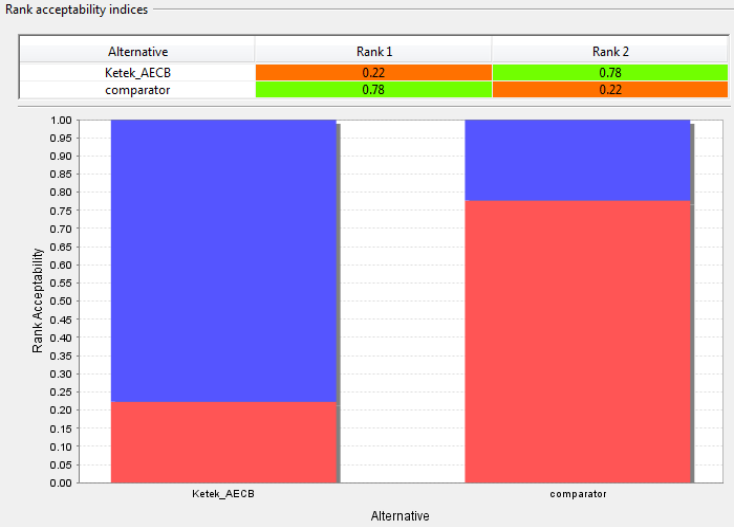
Calculate the value function for each alternative from the samples obtained in Step 1 and mark the alternative with larger value function as winner.

Repeat Step 1 and Step 2 n times (1000000, say) and calculate the number of times each alternative is winner.

Rank acceptability index for each alternative is approximated by the number of times (the alternative is winner) divided by total run number 900000.

The results are shown below

Figure 4.2.2-6: Rank acceptability of Ketek and its comparator under missing weights



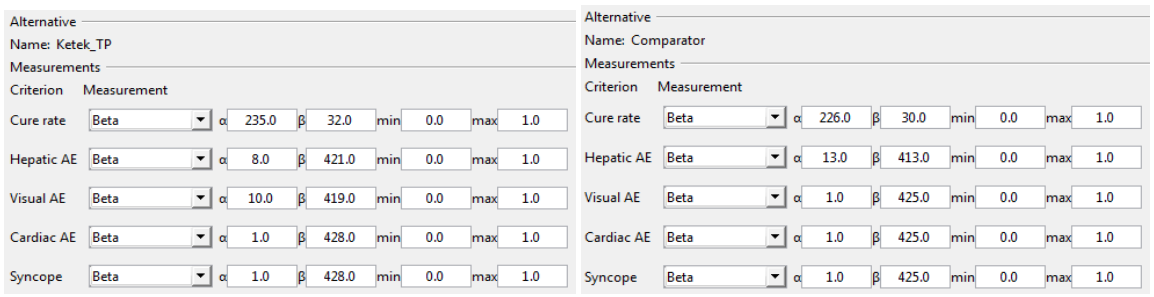
The conclusion by missing weights is still that Ketek is worse than its comparator.

4.2.2.3.2 Tonsillitis/Pharyngitis (TP)

Analysis and results

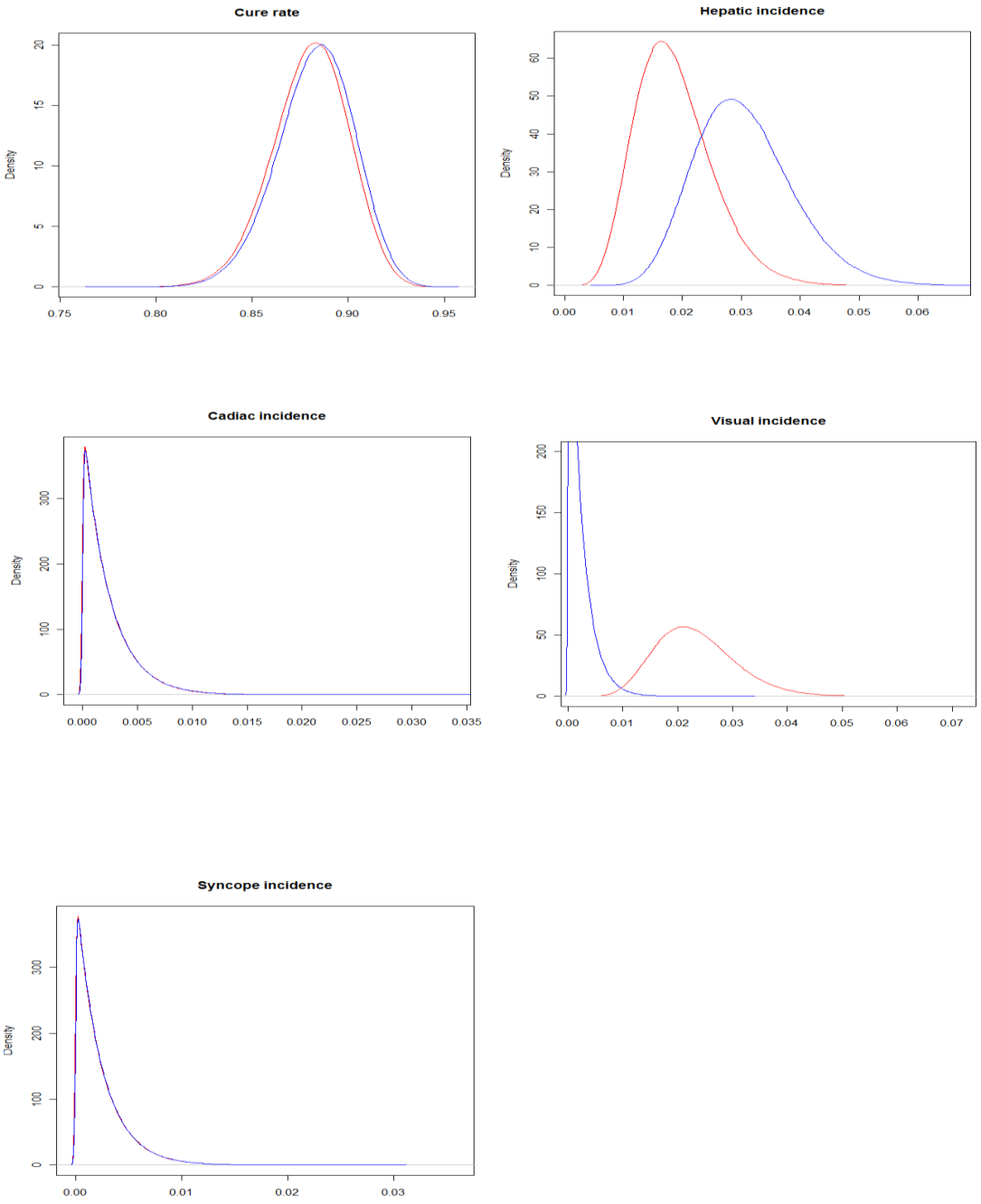
Criteria evaluation for each alternative: In this analysis, a Bayesian approached is adopted to derive the distributions for all alternatives on all criteria. For TP cure rate, from non-informative prior Beta(1,1), the distribution of cure rate is updated from observed rates in two phase III clinical studies. The distribution of incidence of AE of each body system is updated from non-informative prior Beta(1,1) with pooled data. The resulting posterior distributions of all criteria for Ketek and its comparator are listed as the following.

Figure 4.2.2-7: Distributions of Ketek and its comparator on all criteria



Graphic presentations of these distributions are given below.

Figure 4.2.2-8: Distributions of Ketek (red) and its comparator (blue) on all criteria

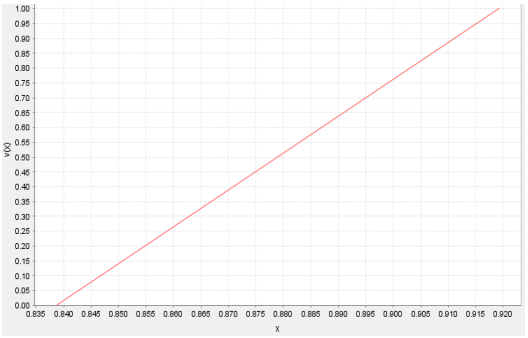


Utility

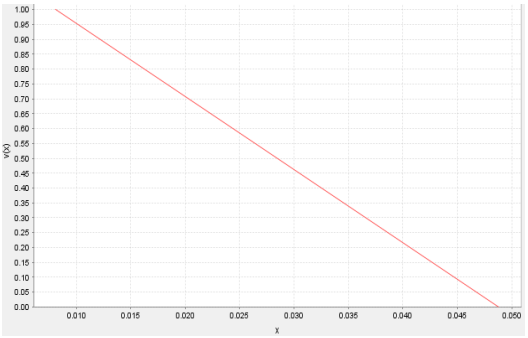
In this analysis we use linear utility function. The least preferred value and most preferred value of the benefit criterion are the lower end and upper end of 95%CI for both alternatives (software default). The least preferred value and most preferred value of each risk criterion are the upper end and lower end of 95%CI for both alternatives. The shape of utility function for each criterion is presented below

Figure 4.2.2-9: Utility function by criteria

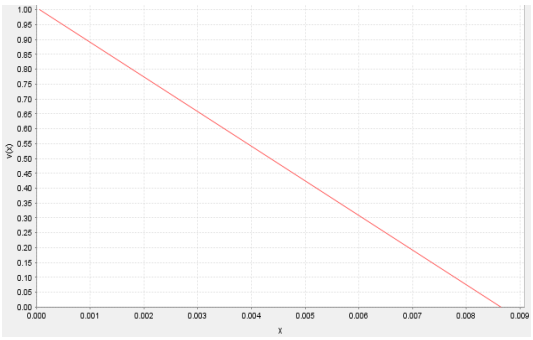
Cure rate



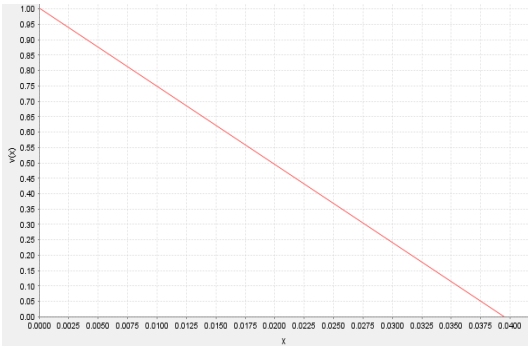
Hepatic incidence



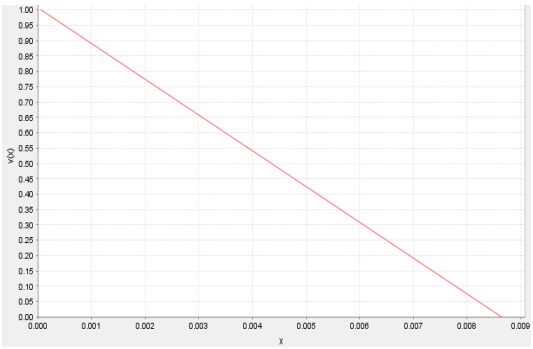
Cardiac incidence



Visual incidence



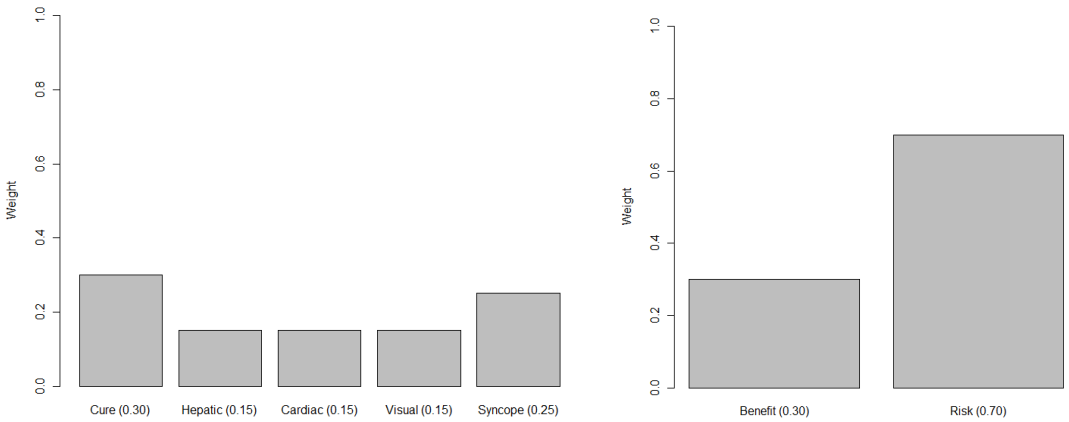
Syncope incidence



Value function and choice of weights

The value function, which represents the balance of benefit and risk, is weighted sum of utilities over all criteria. The choice of weights in this analysis is shown below

Figure 4.2.2-10: Weights cross the five criteria and benefit, risk total



Ranking the options

In SMAA, the so-called rank acceptability index for an alternative is the probability that this alternative has the largest value function among all alternatives. The rank acceptability index of Ketek and its comparator is calculated through simulation means from the posterior distributions of the criteria using jsmaa software. The simulation goes through the following steps:

From posterior distribution of each alternative on each criterion, a random sample is drawn. Each alternative thus has sampled values on all criteria.

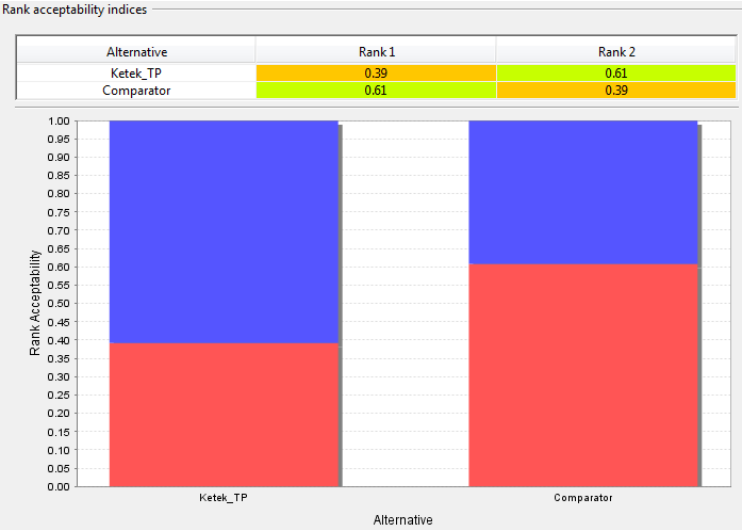
The value function for each alternative is calculated from the samples in Step 1 (convert them into utility and then calculating the weighted sum of utility). The alternative with larger value function is recorded as winner.

Repeat Step 1 and Step 2 n times (1000000, say) and calculate the number of times each alternative is winner.

Rank acceptability index for each alternative is calculated by the number of times (the alternative is winner) divided by total run number n.

The resulting rank acceptability index is shown below.

Figure 4.2.2-11: Rank acceptability of Ketek and its comparator



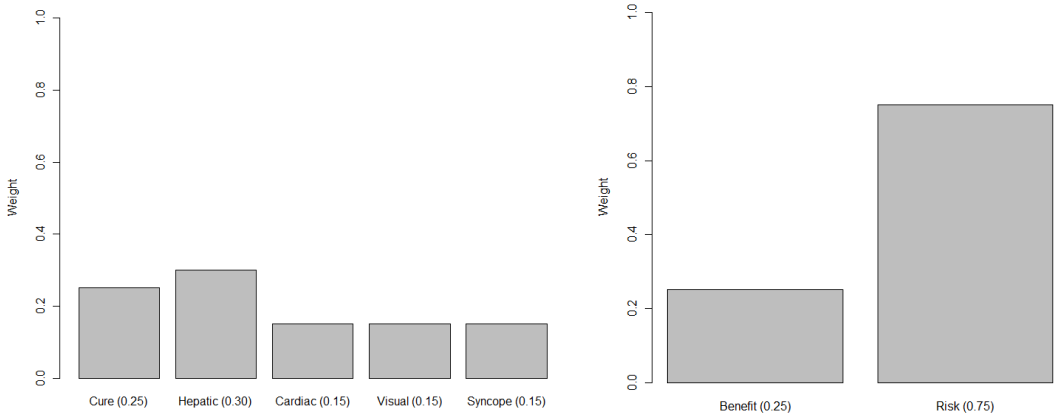
The conclusion is then: Ketek is worse than its comparator.

Sensitivity analysis by increasing weight on hepatic AE

New weight on hepatic AE

Hepatic AE is the criterion where Ketek performs better than its comparator. We increase the weight of hepatic incidence to 0.3, while lower the weight on cure rate to 0.25. See figure below for the new weights.

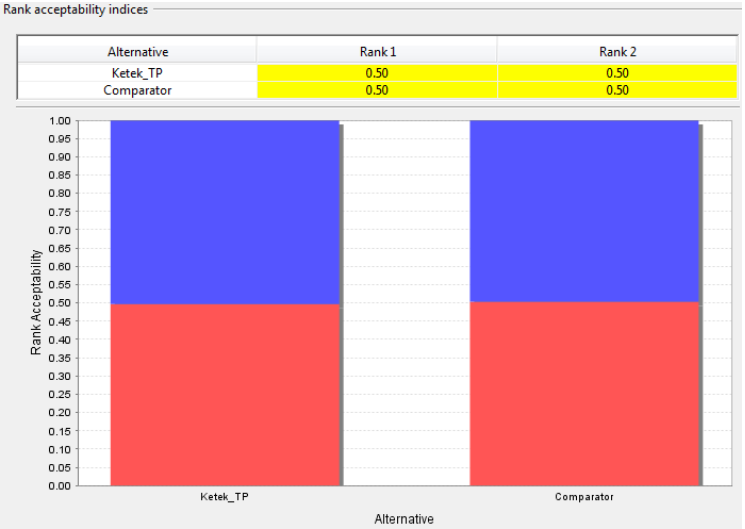
Figure 4.2.2-12: New weights cross the five criteria and benefit, risk total



Ranking under new weights

The results from the above new weight assignment are shown below

Figure 4.2.2-13: Rank acceptability of Ketek and its comparator under new weights



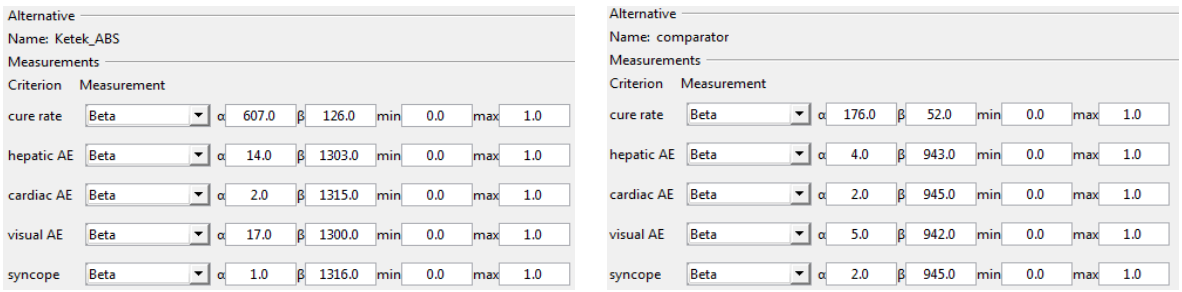
The two alternatives under new weight assignment have no advantage over each other. If the weight on hepatic AE is further increased, Ketek is going to be better than its comparator.

4.2.2.3.3 Acute bacterial sinusitis (ABS)

Analysis and results

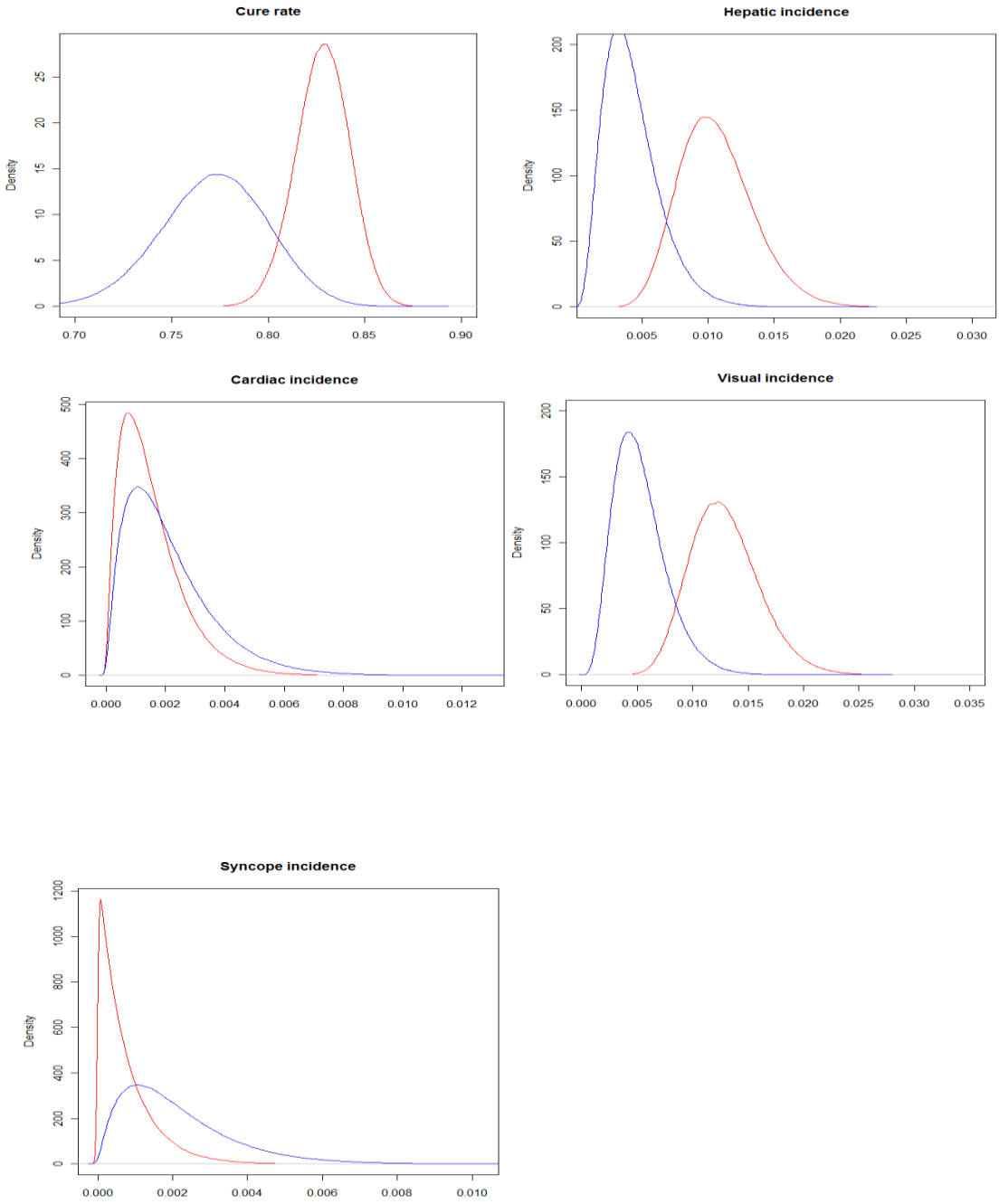
Criteria evaluation for each alternative: In this analysis, a Bayesian approached is adopted to derive the distributions for all alternative on all criteria. For ABS cure rate, from non-informative prior Beta(1,1), the distribution of cure rate is updated from observed rates in three phase III clinical studies. The distribution of incidence of AE of each body system is updated from non-informative prior Beta(1,1) with pooled data. The resulting posterior distributions of all criteria for Ketek and its comparator are listed as the following.

Figure 4.2.2-14: Distributions of Ketek and its comparator on all criteria



Graphic presentations of these distributions are given below.

Figure 4.2.2-15: Distributions of Ketek (red) and its comparator (blue) on all criteria



Utility

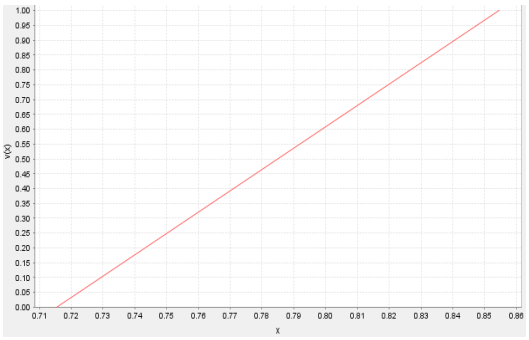
Utility of each criterion is a monotone function taking value in range [0,1] with 0 for the least preferred value and 1 for the most preferred value. Outside the most preferred and least preferred, the utility keeps as 1 and 0.

In this analysis we use linear utility function. The least preferred value and most preferred value of the benefit criterion are the lower end and upper end of 95%CI for both alternatives (software default). The least preferred value and most preferred value of each risk criterion are the upper end

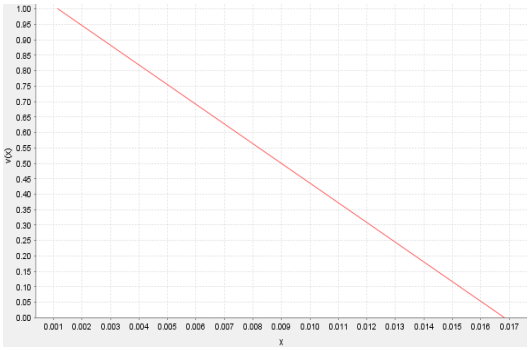
and lower end of 95%CI for both alternatives. The shape of utility function for each criterion is presented below

Figure 4.2.2-16: Utility function by criteria

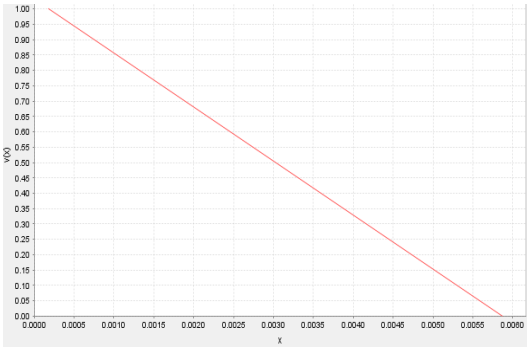
Cure rate



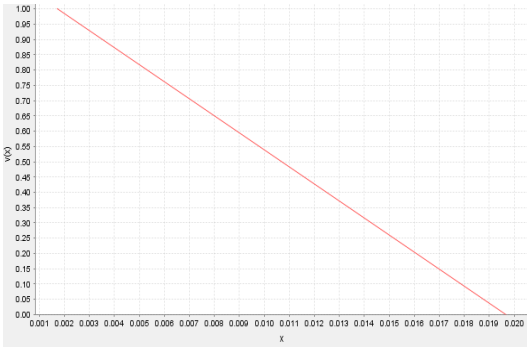
Hepatic incidence



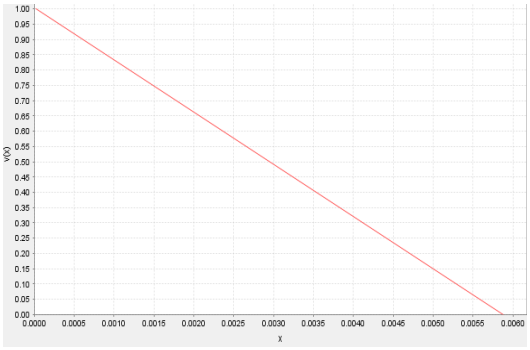
Cardiac incidence



Visual incidence



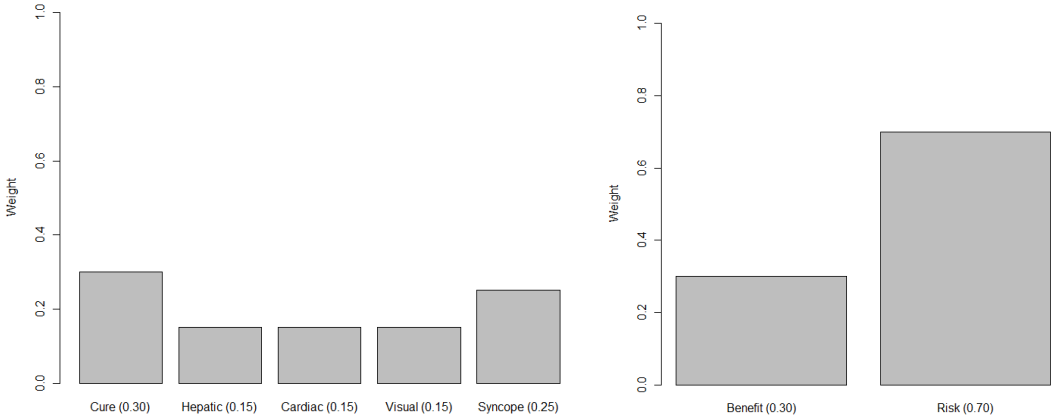
Syncope incidence



Value function and choice of weights

The value function, which represents the balance of benefit and risk, is weighted sum of utilities over all criteria. The choice of weights in this analysis is shown below

Figure 4.2.2-17: Weights cross the five criteria, benefit and risk total



Ranking the options

In SMAA, the so-called rank acceptability index for an alternative is the probability that this alternative has the largest value function among all alternatives. The rank acceptability index of Ketek and its comparator is calculated through simulation means from the posterior distributions of the criteria using jsmaa software. The simulation goes through the following steps:

From posterior distribution of each alternative on each criterion, a random sample is drawn. Each alternative thus has sampled values on all criteria.

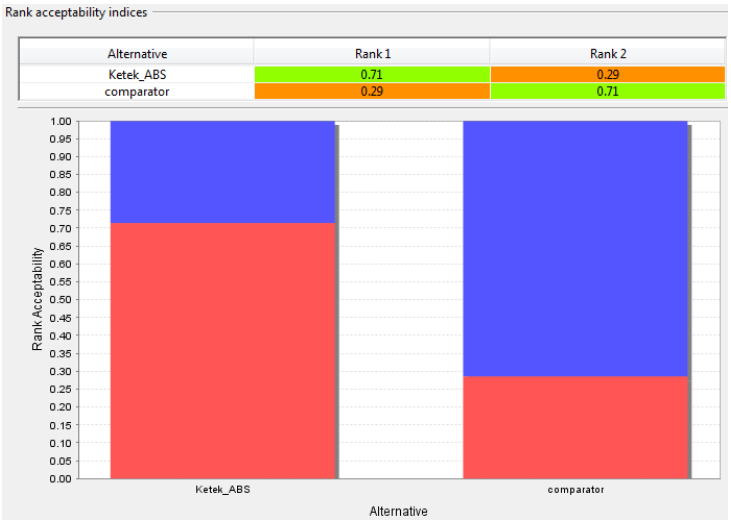
The value function for each alternative is calculated from the samples in Step 1 (convert them into utility and then calculating the weighted sum of utility). The alternative with larger value function is recorded as winner.

Repeat Step 1 and Step 2 n times (1000000, say) and calculate the number of times each alternative is winner.

Rank acceptability index for each alternative is calculated by the number of times (the alternative is winner) divided by total run number n.

The resulting rank acceptability index is shown below.

Figure 4.2.2-18: Rank acceptability of Ketek and its comparator



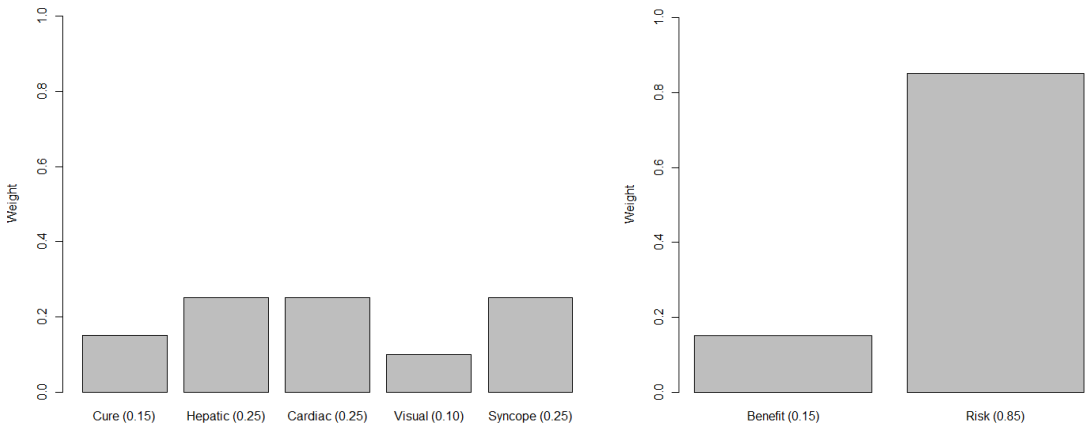
The conclusion is then: Ketek is better than its comparator.

Sensitivity analysis by increasing weight on hepatic and visual AE

New weight on hepatic AE

Hepatic AE and visual AE are the two criteria where comparator performs better than Ketek. We increase the weights of hepatic incidence and visual incidence to 0.25, while lower the weight on cure rate to 0.15. See figure below for the new weights.

Figure 4.2.2-19: New weights cross the five criteria and benefit, risk total



Ranking under new weights

The results from the above new weight assignment are shown below

Figure 4.2.2-20: Rank acceptability of Ketek and its comparator under new weights

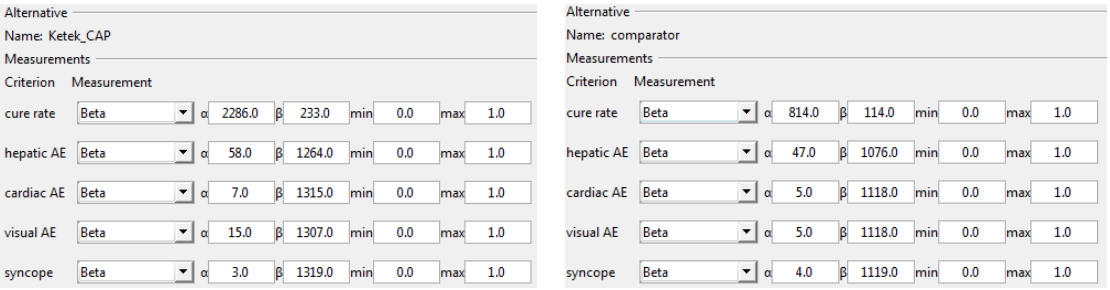
The two alternatives under new weight assignment have no advantage over each other. If the weights on hepatic AEs or visual AEs are further increased, Ketek is going to be worse than its comparator.

4.2.2.3.4 Community-Acquired Pneumonia (CAP)

Analysis and results

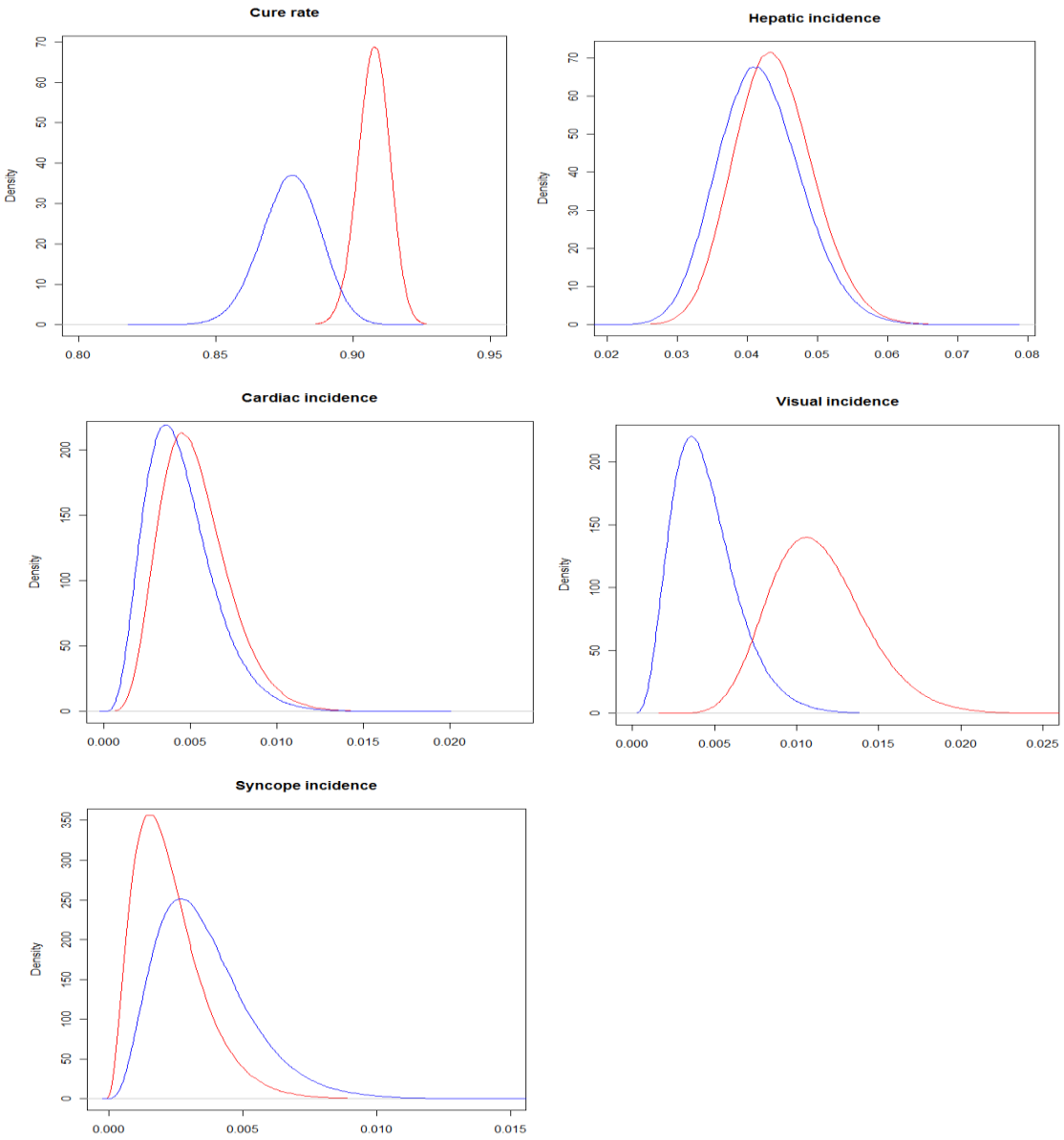
Criteria evaluation for each alternative: In this case study, a Bayesian approached is adopted to derive the distributions for all alternatives on all criteria. For CAP cure rate, from non-informative prior Beta(1,1), the distribution of cure rate is updated from observed rates in eight clinical studies. The distribution of incidence of AE of each body system is updated from non-informative prior Beta(1,1) with pooled data. The resulting posterior distributions of all criteria for Ketek and its comparator are listed as the following.

Figure 4.2.2-21: Distributions of Ketek and its comparator on all criteria



Graphic presentations of these distributions are given below.

Figure 4.2.2-22: Distributions of Ketek (red) and its comparator (blue) on all criteria

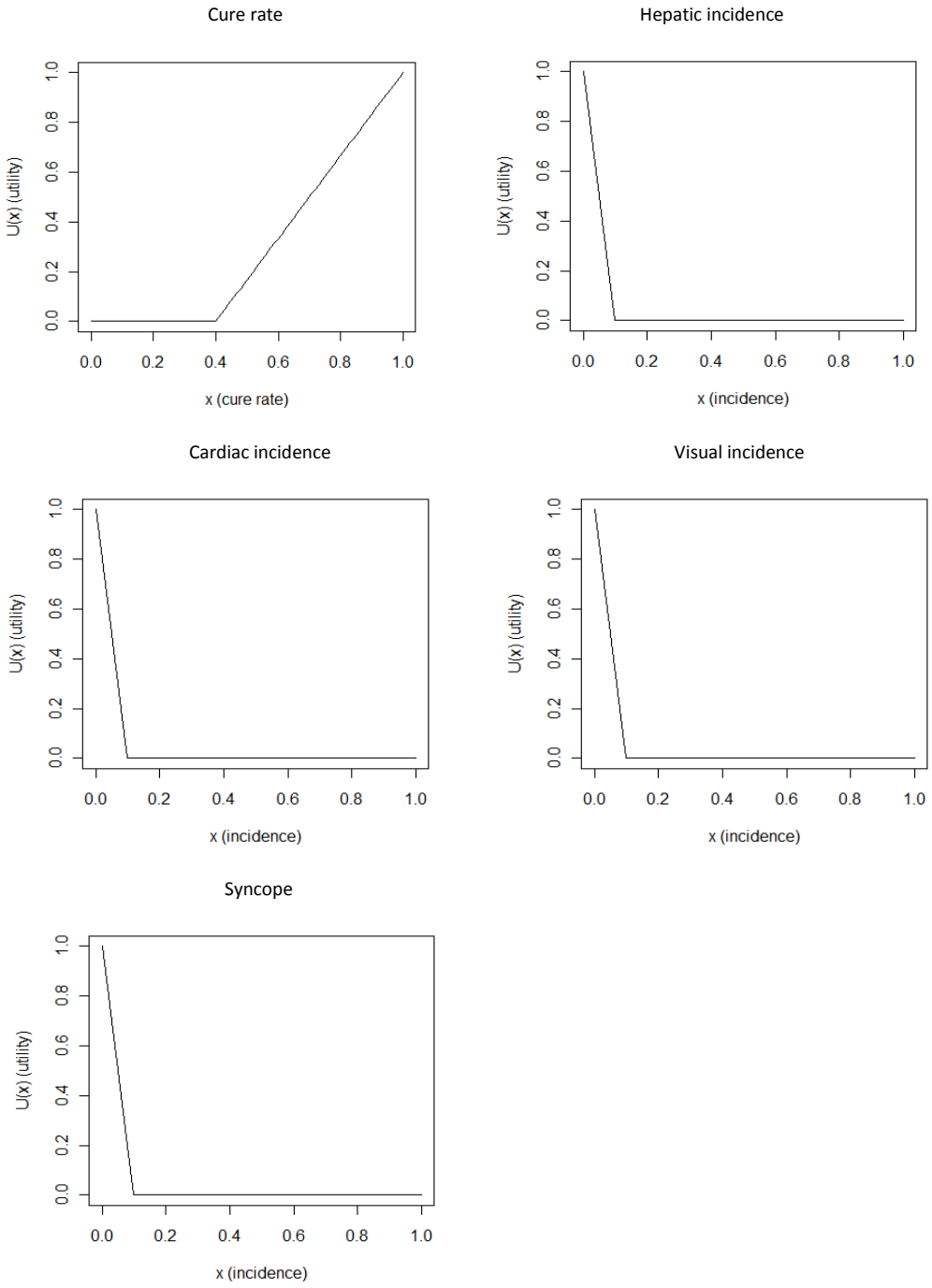


Utility

Utility of each criterion is a monotone function taking values in range [0,1] with 0 for the least preferred value and 1 for the most preferred value. Outside the most preferred and least preferred, the utility keeps as 1 and 0.

For cure rate, the least preferred value is 40% (cure rate less than 40% has 0 utility), the most preferred value is 100%. The utility is linear between the least preferred and most preferred. For AE incidence, the least preferred value is 1% (incidence over 1% has 0 utility), the most preferred value is 0%. The utility is linear between the least preferred and most preferred. Graphic presentations of utility function are shown below

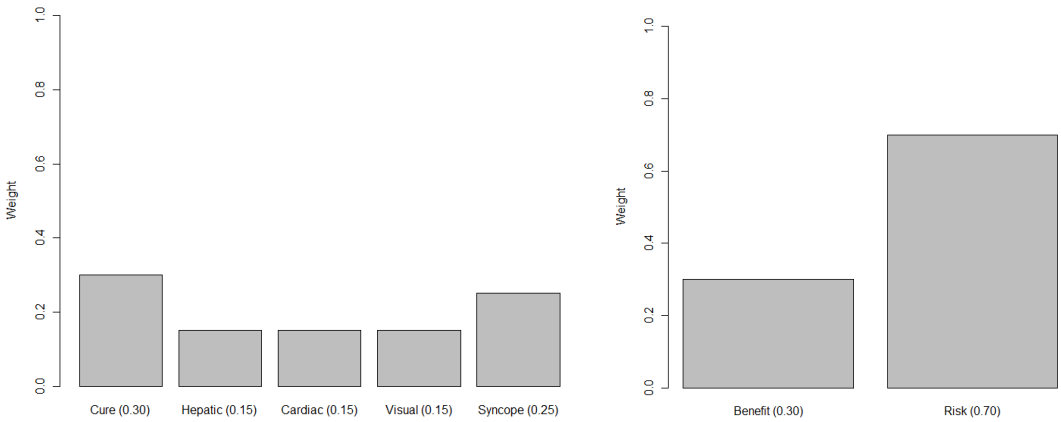
Figure 4.2.2-23: Utility functions by criteria



Value function and choice of weights

The value function, which represents the balance of benefit and risk, is weighted sum of utilities over all criteria. The choice of weights in this analysis is shown below

Figure 4.2.2-24: Weights cross the five criteria, benefit and risk total



Ranking the options

In SMAA, the so-called rank acceptability index for an alternative is the probability that this alternative has the largest value function among all alternatives. The rank acceptability index of Ketek and its comparator is calculated through simulation means from the posterior distributions of the criteria. The simulation goes through the following steps:

From posterior distribution of each alternative on each criterion, a random sample is drawn. Each alternative thus has sampled values on all criteria.

The value function for each alternative is calculated from the samples in Step 1 (convert them into utility and then calculating the weighted sum of utility). The alternative with larger value function is recorded as winner.

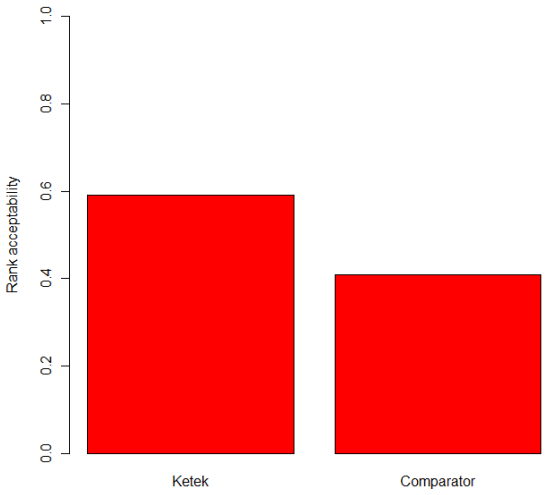
Repeat Step 1 and Step 2 900000 and calculate the number of times each alternative is winner.

Rank acceptability index for each alternative is calculated by the number of times (the alternative is winner) divided by total run number 900000.

The resulting rank acceptability index is shown below.

Figure 4.2.2-25: Rank acceptability of Ketek and its comparator

Alternative	Rank 1	Rank 2
Ketek_CAP	0.5908	0.4092
Comparator	0.4092	0.5908



The conclusion is then: Ketek is better than its comparator.

Sensitivity analysis by means of missing weights

Missing weights

We choose missing weights for a sensitivity analysis. Missing weight means any weight assignment to the five criteria is equally likely. In the terminology of probability, this means weight vector is uniformly distributed in the weight space (a simplex in 5 dimensional Euclid space).

Ranking the options under missing weights

Under the missing weigh setting, the rank acceptability index of Ketek and its comparator is calculated through simulation means from the posterior distributions of the criteria and uniform distribution of weights. The procedure is

Draw a random sample from posterior distribution of each alternative on each criterion. Each alternative then has sampled values on all criteria. Draw a random sample of weight vector from uniform distribution on weight space (5 components sum up to 1).

Calculate the value function for each alternative from the samples obtained in Step 1 and mark the alternative with larger value function as winner.

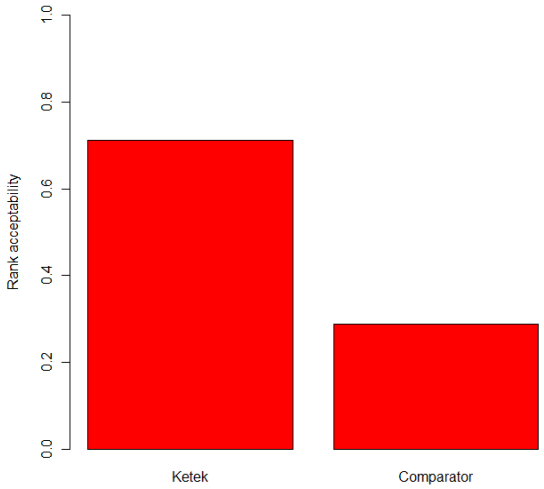
Repeat Step 1 and Step 2 n times (1000000, say) and calculate the number of times each alternative is winner.

Rank acceptability index for each alternative is approximated by the number of times (the alternative is winner) divided by total run number 900000.

The results are shown below

Figure 4.2.2-26: Rank acceptability of Ketek and its comparator under missing weights

Alternative	Rank 1	Rank 2
Ketek_CAP	0.7121	0.2879
Comparator	0.2879	0.7121



Ketek is still better than its comparator.

4.2.2.4 Comments on SMAA in this study

4.2.2.4.1 Applicability and acceptability

(1) SMAA extends MCDA by bringing in analysis the sampling variation and preference uncertainty, which are almost inevitable in real practices. This method is applicable to any problem that MCDA is applicable.

(2) The utility used in SMAA and MCDA can be very general. If a decision maker is not

sure about the 'satisfaction' (utility) on criteria and would like to use the actual measurements in the criteria, he may simply use the linear utility function (by some scale normalization if necessary).

(3) The weights can be exact, or in a range, or missing, which means any assignments of weights are equally likely. After the analysis, SMAA will tell what assignment of weights favour which alternative. This flexibility is extremely helpful to decision maker.

4.2.2.4.2 Problems in implementation

(1) Software for SMAA is still in development stage and choices (utility functions, choices of most preferred and least preferred values etc) are limited.

(2) The process of preference elicitation (utilities and weights) is not entirely clear. Is decision conference enough?

(3) In simulations, criteria are assumed to be independent of each other. It is not clear how much the correlation affect the results. This may not be a consequence of SMAA, but an aspect deserving further investigations.

4.3 Metric Indices

4.3.1 Benefit-Risk Ratio (BRR)

See section 4.4.1 Probabilistic Simulation Method (PSM).

4.4 Estimation Technique

4.4.1 Probabilistic Simulation Method (PSM)

4.4.1.1 Objectives

The overall objectives of this analysis are:

To assess the feasibility and suitability of using visualization (risk-benefit plane (RBP), risk-benefit acceptability curve (RBAC)) and estimation techniques (Probabilistic Simulation model (PSM)) for benefit-risk assessment of drugs by the regulator, using Ketek as an example;

The objective is to evaluate the benefit-risk balance of Ketek at marketing authorisation approval using a combination of metric indices, visualization (RBP, RBAC) and estimation techniques (PSM).

4.4.1.2 Development of Probabilistic Simulation model

4.4.1.2.1 Decision context/ Benefit & Risk Criteria

The decision context is about the selection between 'Ketek' and 'Comparator' for ABS indication. The benefit element is cure; the risk element is overall incidence of adverse event of special interest-AESI (Hepatic, Cardiac, Syncope and Visual). Data for analysis were obtained from pooled randomized controlled Phase III trials of Ketek vs. comparator.

4.4.1.2.2 Calculation of Benefit Risk Ratio

The BRR is the ratio of the difference in benefit to difference in risk, or equivalently, the ratio of Number Needed to Harm (NNH) to Number Needed to Treat (NNT):

$$BRR = \frac{pk - pc}{qk - qc}$$

where pk and pc are the probabilities of benefit in the ketek treatment and comparator arms, respectively, and qk and qc are the probabilities of risk in the ketek treatment and comparator arms, respectively. The BRR can be interpreted as the increase in the number of expected patients who will

benefit for each additional adverse event that is incurred from using the ketek treatment rather than the comparator.

4.4.1.3 Simulation Model & BR Visualization

First, we develop a probabilistic model that incorporate the uncertainty around both the risks and benefits simultaneously by specifying probability distributions for each model parameter to represent their uncertainty. Next, a Monte Carlo simulation (MCS) is run, which randomly selects values from each specified distribution, allowing the joint uncertainty of the risks and benefits to be considered. Two MCS methods were explored. The first method simulates the proportion of benefit and risk for each treatment arm derived from the pooled Phase III clinical trial using Beta distribution 4, and incremental probabilities were calculated. The second method simulates the difference of proportion using bivariate normal distribution 5. For both analyses, we assume risk and benefit vary independently since no correlational data is available. Our simulations were run 5000 times.

4.4.1.4 Results

The incremental risk–benefit pairs from 5,000 simulations (with 95% confidence ellipse) for ABS indications are presented on a RBP (an array and visualization of the simulated joint density of incremental risks and benefits illustrated on an x–y scatterplot) with ellipse confidence interval to help assess the uncertainty around the risks and benefits (Figure 4.4.1-1). Most of the 5,000 points fell in the NE/SE quadrant, indicating a greater chance that Ketek is more effective and with lower risk than the comparator for ABS indication.

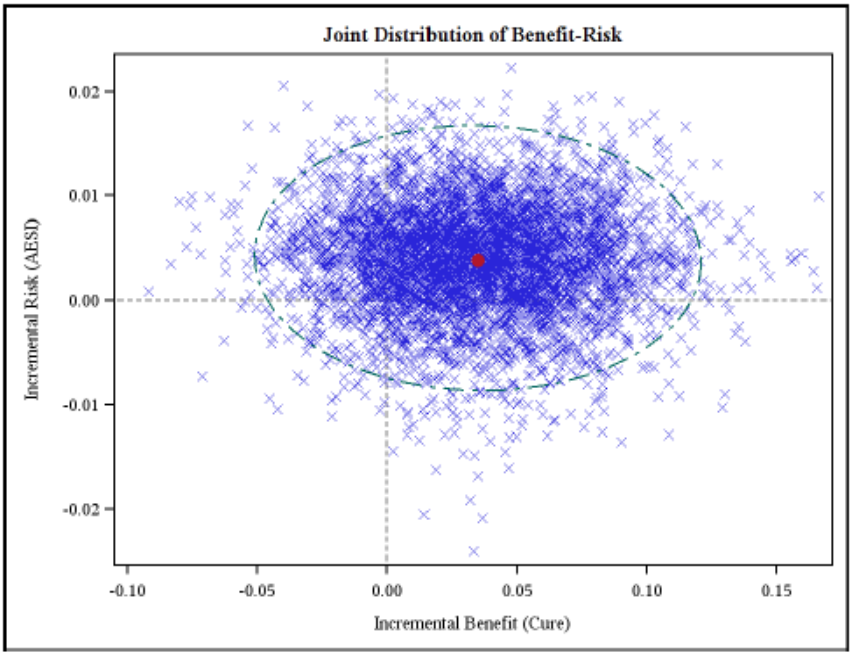


Figure 4.4.1-1: Results of the Monte Carlo simulation for ABS indication plotted on the risk–benefit plane: the incremental probability of AESI (Hepatic, Syncope, Visual Cardiac) vs. the incremental probability of Cure, with 95% confidence interval. The red dot mark the point estimate of BRR of Ketek vs comparator. Because the benefit increases from left to right along the x-axis, positive values (to the

right of the vertical axis) represent greater benefits with the Ketek treatment. Similarly, positive Y-coordinates indicate a greater probability of the risk for the Ketek treatment.

To accommodate different risk preferences, the results are also illustrated in Figure 4.4.1-2 using RBAC, which incorporates different risk–benefit acceptability thresholds (μ), or the number of AESI's one is willing to accept per unit benefit (cure). At an acceptability threshold of μ = 0.25 one is willing to accept 1 AESI to avert four ABS and at μ=4, one would accept 4 AESI to avert 1 ABS. If one is willing to accept up to 1 SAE to avert 4 ABS (μ= 0.25), there is a 81% chance that Ketek provides a net benefit. There is also 96% chance that the risk–benefit ratio is less than 1 (i.e., 96% of the points fall below μ= 1). Correspondingly, there is a 4% probability that the number of AESI's induced by Ketek is greater than the number of ABS's averted.

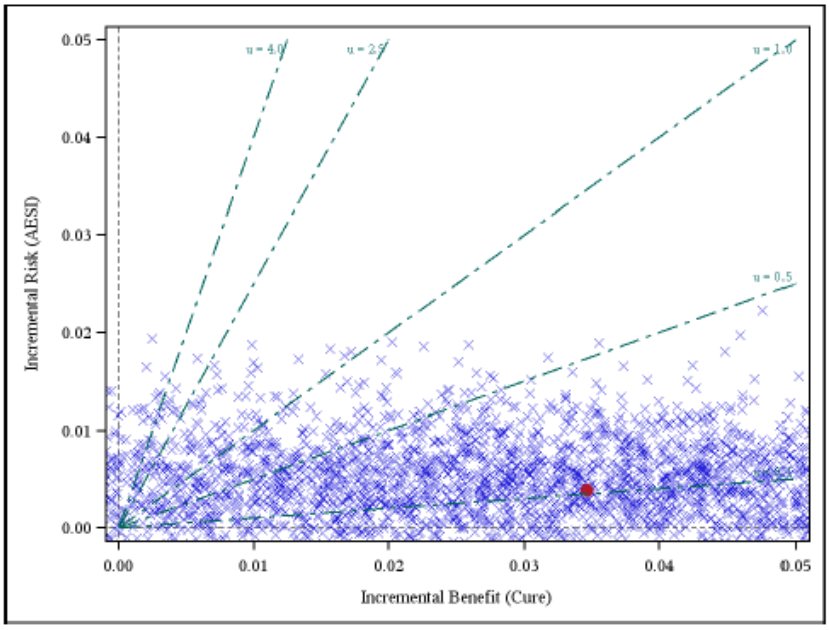


Figure 4.4.1-2: Incremental risk (AESI:Hepatic, Cardiac, Syncope, Visual) versus incremental benefit (Cure) for ABS indication plotted on the RBP and varying acceptability threshold obtained by probabilistic simulation.

Figure 4.4.1-3 shows RBAC for the probability that Ketek is net-beneficial relative to comparator at any risk–benefit acceptability threshold. If preferences were such that one is willing to accept 1 AESI to prevent 1 ABS, the probability that Ketek provides a net benefit is 0.96.

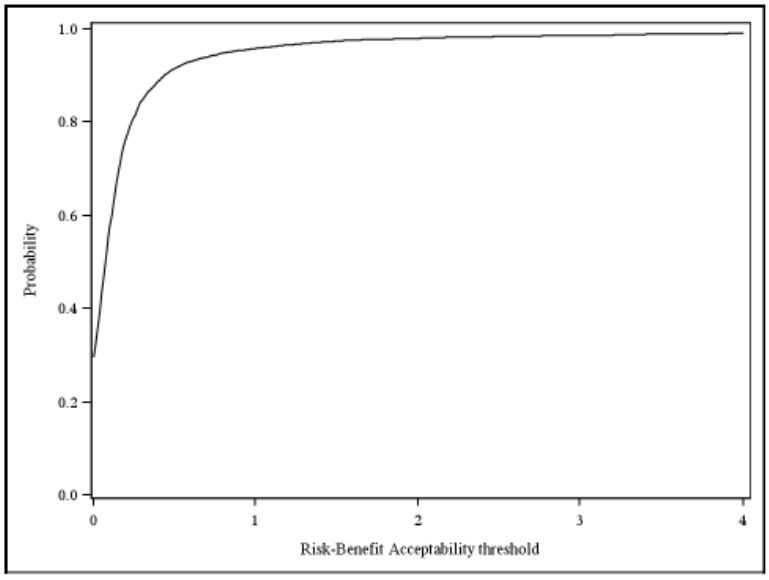


Figure 4.4.1-3: Risk–benefit acceptability curve for the probability that Ketek is net-beneficial relative to comparator at any risk–benefit acceptability threshold. For example, if preferences were such that one is willing to accept 1 Hepatic event to gain cure rate by 1, the probability that Ketek provides a net benefit is 0.96.

4.4.1.5 Appraisal

4.4.1.5.1 Applicability and acceptability

The methods described here (RBP, RBAC and PSM) are applicable to all decision problems to which benefit-risk ratio (BRR) is calculated. The methods provide the necessary visualization and representation of benefit and risk information and incorporate uncertainty into analysis. Simple benefit-risk models based on limited data summaries may require only basic estimation techniques, but more sophisticated methods, or multiple sources of data require more complex estimation techniques. In health care settings, the decision maker is faced with having to make value- or preference-based treatment decisions under uncertainty. Both the risk-benefit joint distribution plot and acceptability curves helps decision maker to trade-off risk and benefit.

4.4.1.5.2 Problems in implementation

Potential problems in applying the techniques include collapsing benefits and risks into single measures (i.e. BRR). Because of two-dimensional model for RBP, it is unclear how one might incorporate multiple dimensions of risks and benefits. The approach is suitable for two therapies for a binary measure of benefit and a binary measure of risk.

For this analysis SAS software was used to compute the BRR, RBP, RBAC and PSM and all posterior probabilities, but these computations also can be done using softwares such as R, SPLUS and Excel.

4.5 Other Technique Used

4.5.1 Sarac's Benefit-Risk Assessment Methodology (SBRAM)

4.5.1.1 Decision context

4.5.1.1.1 Aim

The aim of this assessment is to judge whether the benefit risk profile of Ketek is satisfactory for market authorisation in the following indications

In Patient of 18 years and older:

- Community-acquired pneumonia, mild or moderate (CAP)
- Acute exacerbation of chronic bronchitis (AECB)
- Acute sinusitis (ABS)

In Patient of 12 years and older:

- Tonsillitis/pharyngitis (TP) cause by Group A beta streptococci, as an alternative when beta-lactam antibiotics are not appropriate

And whether any of the indications should approved with restriction

The assessment will be made with the perspective of the regulators, weights on relevant assessment criteria will be given by Sinan B Sarac, MD.

An assessment will be made for each of the four indications, however to supplement the assessment per indication an assessment of the overall risk will be made (excluding TP as the only indication which uses penicillin as comparator).

Several alternative treatments are registered for the four indications

- CAP: Amoxicillin, Clarithromycin, Trovafloxacin
- AECB: Amoxicillin-clavulanic acid, Cefuroxime, Clarithromycin, Azithromycin
- ABS: Amoxicillin-clavulanic acid and Cefuroxime
- TP: Penicillin, clarithromycin

All alternatives, except Azithromycin, have been used as comparator in the different Phase III trails for the relevant indications.

If the benefit risk profile for one or more of the indication is not considered sufficiently positive to grant market authorisation, additional assessment will be made to consider the benefit risk profile for the indication with restricted use (iterative process). Technically this is only possible for the indication CAP due to limitations in data.

Drug information

See 4.1.1 PrOACT-URL – Problem for drug information on Ketek,

4.5.1.1.2 Data source

Data for assessment of Ketek were obtained from phase III and IV trials, published in the EPAR, see section 4.1.1 PrOACT-URL for description of data. All date used in this assessment are from EPAR:

EMEA/H/C/354/A22/41, London, 30 Marts, 2007. A more detailed overview of data can be found in section 8.4 Appendix A: Data on Ketek from EPAR.

Use of data:
Efficacy data from phase III including open label and phase IV will be pooled for the analysis, analysing all telithromycin treated versus all comparator treated, for each indication. This will be done to the extent possible based on the information available in the EPAR, which does not include data from all phase IV studies. This is done since safety data are already pooled, in the EPAR, although pooled phase III double-blind, pooled open-label and pooled phase IV data are given separately.

4.5.1.1.3 Expectations

It is expected that the benefit risk balance for Ketek will be positive for all four indication, and the market authorisation can kept without restriction.

4.5.1.2 Benefit and Risk Criteria within the Decision Context

4.5.1.2.1 Benefit Criteria

- Cure
- PERPs at TOC (for indication AECB)

4.5.1.2.2 Risk Criteria

- TEAEs
- SEAs
- Hepatic EAs
- Cardiac EAs
- Visual EAs
- Syncope

4.5.1.3 Weighting

All benefit and risk criteria are weighted on a scale of one, two and three. One is given to the criteria of lowest importance to the overall assessment and three is given to the criteria of high importance to the overall assessment. The weights for all criteria and justification for the assigned weight is displayed in Table 4.5.1-1. The weighting is the same for all indications.

Table 4.5.1-1: Weighting of benefit and risk criteria.

Criterion	Justification	*Weight*
Cure	This is primary endpoint for all antibiotics.	*3*
Syncope	There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome.	*2*
Visual	Visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances include blurred vision, difficulty focusing, and diplopia. Most events are mild to moderate; however, severe cases have been reported.	*1*

Cardiac	Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (e.g., quinidine and procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents. Cases of torsades de pointes have been reported post-marketing with KETEK. In clinical trials, no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical trials, including 204 patients having a prolonged QTc at baseline	*2*
SAE	There exist several other antibiotics for the same indications. Therefore any tendency showing an unfavourable number of SAE for Ketek will be highly concerning.	*3*
Hepatic	Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK.	*3*
TEAE	*These type events are rarely related to the drug it self. However, safety surveillance could reveal potentially related events.*	*1*

Ref: Ketek.com

4.5.1.4 Scoring

All data describing the stated criteria are discrete and can be scored using the SBRAM confidence interval scoring method, see manuscript posted at eroom, "Balancing benefits and risks – data-driven clinical benefit-risk assessment" Sarac et al. (WP5/WSB/Contributed materials/Methodology materials). All scoring charts can be seen in section 8.5 Sarac's Benefit-Risk Assessment Methodology Appendix B: Scoring Charts.

Scoring is based on $P(X_{Drug} > X_{Comparator}) \geq \alpha$, $\alpha = 2/3$. The value of α can be changed to represent a lower or higher proportion as long as α lies with in] 0.5; 1]. For scoring of Ketek data α = 2/3.

Scoring charts used for scoring of criteria are produced using MATLAB with statistical toolbox.

4.5.1.5 Evaluation of uncertainty and evidence

The evaluation of uncertainty and evidence is done qualitatively, based on the scoring charts (Section 8.5 Sarac's Benefit-Risk Assessment Methodology Appendix B: Scoring Charts). The objective scores of borderline criteria are changed to interval scores.

4.5.1.6 Weighted Scores

Table 4.5.1-2: Weighted scores for all indications

Criterion	Weight	Score				Weighted Score			
		CAP	ABS	AECB	TP	CAP	ABS	AECB	TP
Cure	3	+1	1	0	0	+3	3	0	0
	3	-	-	0-1	-	-	-	0-2	-
Syncope	2	0-1	0-1	-1	0	0-2	0-2	-2	0

Visual	1	-1-0	-1	-1	-1	-1-0	-1	-1	-1
Cardiac	2	0-1	0-1	0-1	0	0-2	0-2	0-1	0
SAE	3	1	-1-0	-1	0	3	-3-0	-3	0
Hepatic	3	1	-1	0	+1	3	-3	0	+3
TEAE	1	1	-1	-1	-1	1	-1	-1	-1

For the interval scores, the bold numbers are the scores based on the score chart.

4.5.1.7 Plots for Visualisation

Tornado-diagram showing the results of benefit risk analyses of Ketek in the indication CAP

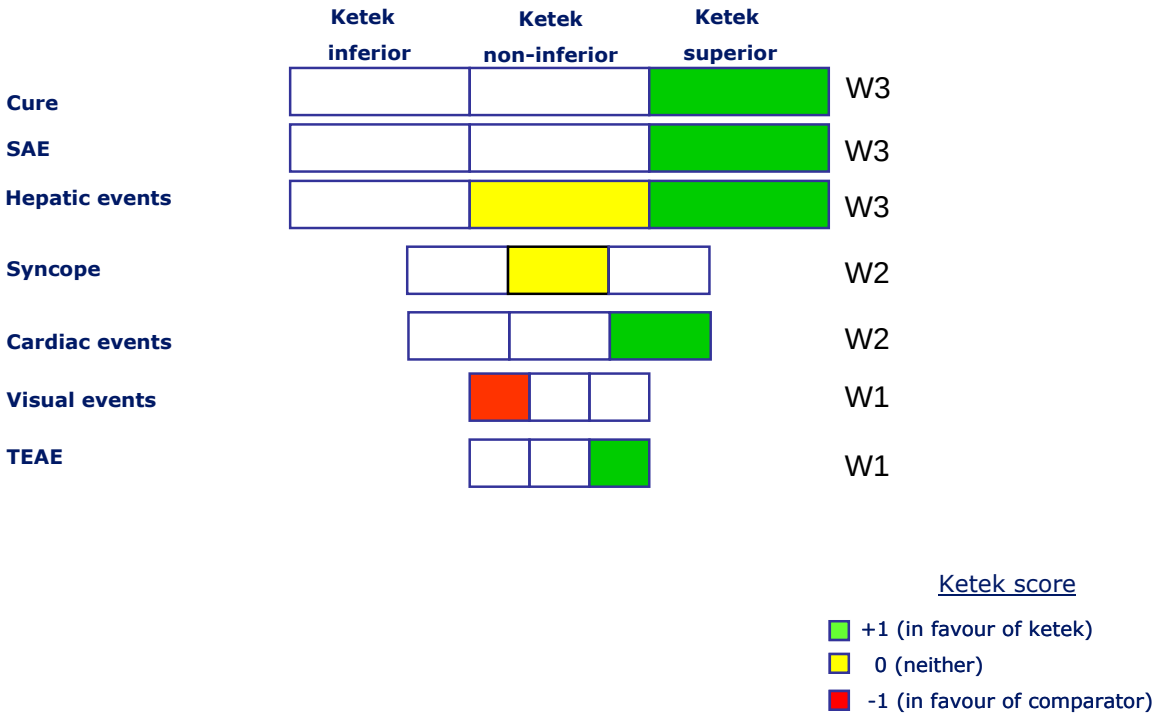


Figure 4.5.1-1: Tornado-diagram CAP

Tornado-diagram showing the results of benefit risk analyses of Ketek in the indication ABS

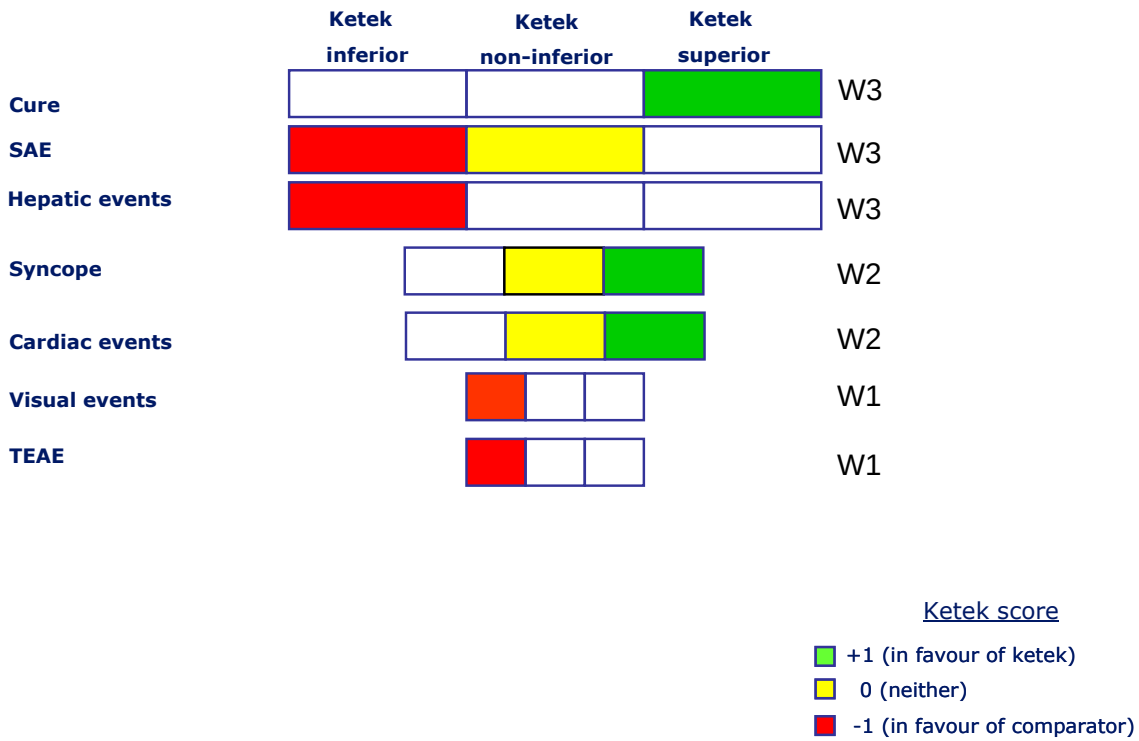


Figure 4.5.1-2: Tornado-diagram ABS

Tornado-diagram showing the results of benefit risk analyses of Ketek in the indication AECB

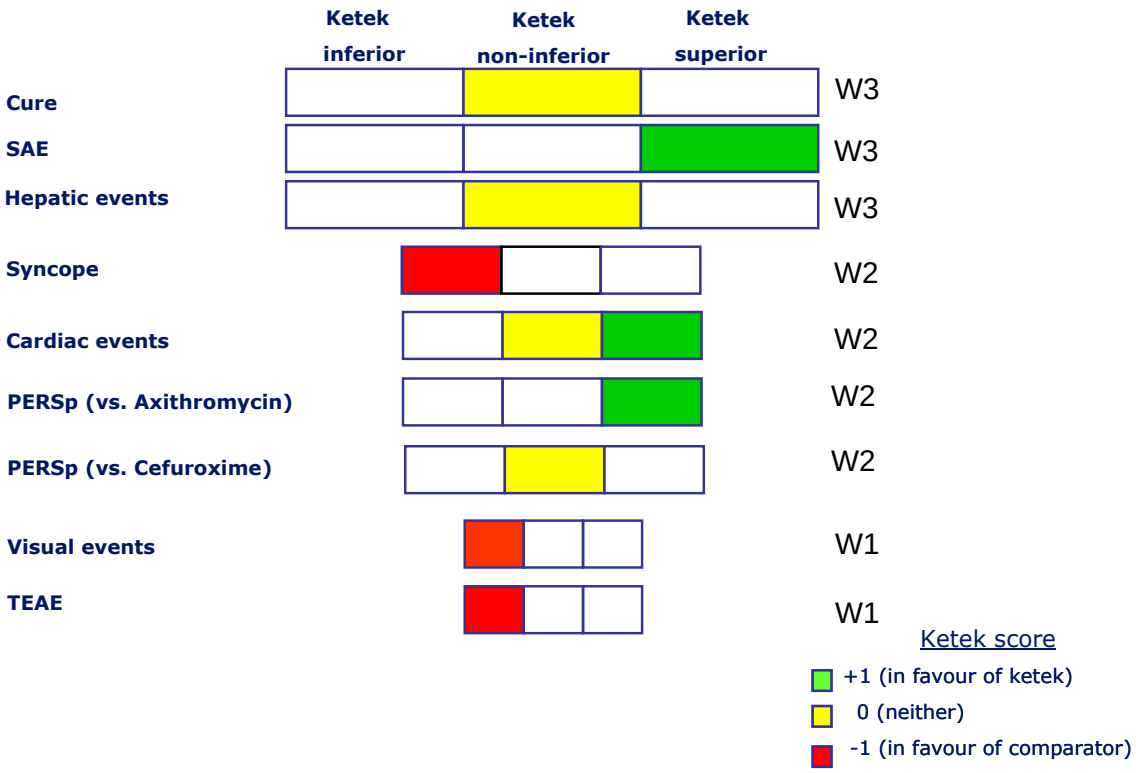


Figure 4.5.1-3: Tornado-diagram AECB

Tornado-diagram showing the results of benefit risk analyses of Ketek in the indication TP

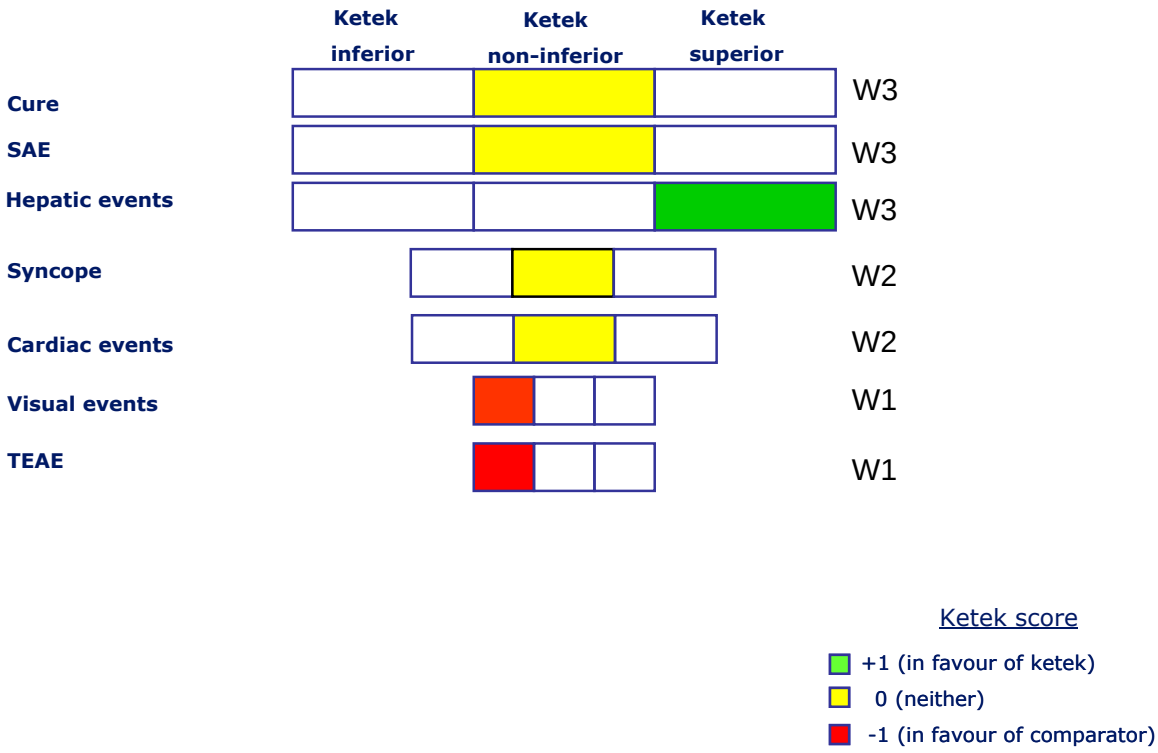
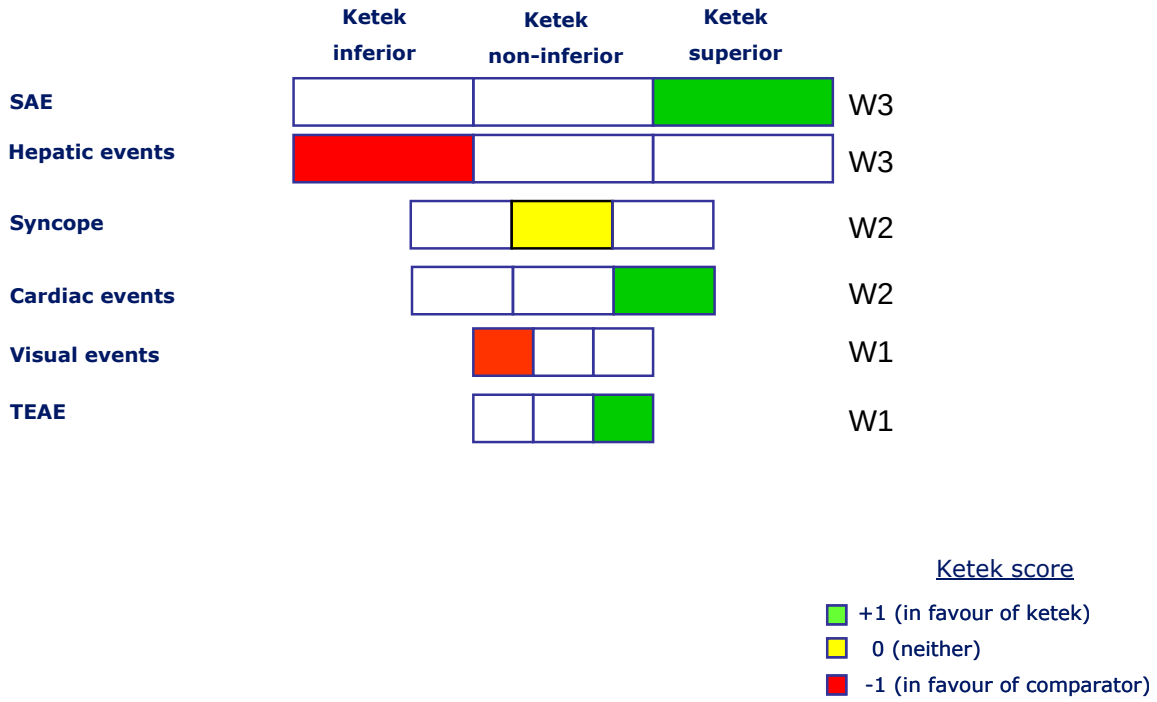


Figure 4.5.1-4: Tornado-diagram TP

Tornado-diagram showing the results of benefit risk analyses on safety parameters for Ketek in indication CAP, ABS and AECB combined



4.5.1.8 Final Benefit Risk Assessment and Conclusion

4.5.1.8.1 Community-acquired pneumonia (CAP)

The high important benefit criteria “cure” was found to be in favour of Ketek. This is also the case for the two high important risk criteria hepatic “AEs” and “SAEs”. Also “cardiac AEs” and “TEAEs” are in favour of Ketek, and “syncope” is not considered being to have any tendency for the drug to be in favour nor in disfavour. The only criteria which are in favour of comparators are “visual AEs”, however this criterion was judged to be of lower importance in this context. Overall the benefit-risk balance of Ketek for the indication CAP is considered positive.

4.5.1.8.2 Acute bacterial sinusitis (ABS)

The high important benefit criteria “cure” was found to be in favour of Ketek. However both high important risk criteria “SAEs” and “Hepatic AEs” was found to be in disfavour for Ketek compared to comparators, also the risk criteria “visual AEs” and “TEAEs” was in disfavour for Ketek, while the analyses of the criteria “syncope” and “cardiac AEs” did not show favour for either Ketek nor comparators. Overall the benefit-risk balance of Ketek for the indication ABS is not considered to be positive

4.5.1.8.3 Acute exacerbation of chronic bronchitis (AECB)

The high important benefit criteria “cure” was found to be not in favour for neither Ketek nor comparators. For the high important criteria “SAEs” is in favour for Ketek, while there are no tendencies towards either drug or comparator for the criteria “Hepatic AEs”. This is also the case for the risk criteria “Cardiac AEs”. While the other medium important risk criteria are in favour for

comparator. The two low important risk criteria are also in favour for comparator. Based on these results the benefit-risk balance for Ketek for the indication AECB is considered to be negative. In the indication of AECB there is data from a phase IV trail on penicillin- or erytromycin-resistant S peneumoniae (PERSp) at TOC (test of cure). For these criteria (Ketek vs. Axithromycin) and (Ketek vs. Ceruroxime) are respectively a favour for Ketek, and no tendency towards difference between Ketek and Cefuroxime

4.5.1.8.4 Thonsillitis/pharyngitis (TP)

To a great extent the analysis shows that there are no tendencies towards any favour of neither Ketek nor comparator for this indication. The high important criteria “Hepatic AEs” is the only criteria that show a tendency towards a favour for Ketek, while both low important criteria “Visual AEs” and “TEAEs” shows a favour for comparator. The benefit-risk profile for Ketek is considered being comparable to comparators.

4.5.1.8.5 Overall conclusions

Ketek has a non-inferior to inferior profile for most indications relative to other comparators, but a superior profile with regard to cure. Therefore, the use of Ketek is advisable in patients were there is failure of other treatments either due to lack of efficacy or risk of bacterial resistance.

Furthermore the overview of Ketek’s performance compared to comparators on the risk criteria combined for all indication (CAB, ABS, AECB), shows that Ketek has a better profile with concern for the criteria SAEs, Cardiac events, and TEAS while it has a worse profile compared to comparators for hepatic and visual events, based on the Sarac Benefit-Risk Method of scoring.

4.5.1.9 Appraisal of SBRAM

Data analysis (scoring) methodology for discrete data uses data direct (trail size, N and number of events x) and the method cannot (in this development stages) accommodate input from Meta-analysis. The scoring for discrete data is based on $P(X_{Drug} > X_{Comparator}) \geq \alpha$, $\alpha = 2/3$. An approximation to the principle of scoring could be developed which uses the probability, p of an event for drug and comparator and the confidence interval for the probabilities. In the SBRAM a scoring approach for continuous data has been described based on $P(X_{Drug} > X_{Comparator}) \geq \alpha$, $\alpha = 2/3$. $P(X_{Drug} > X_{Comparator})$ and may be calculated from the difference distribution, simply as the area under the curve from 0 to infinity.

In the Ketek analysis only two options are identified (i.e. Ketek and comparators, where comparators cover several antibiotic authorised for the indications). This is due to limitations in available data. However the SBRAM compares two option at a time, if several options has to be assessed with the same set of benefit and risk criteria and weighting.

In connection to the decision whether to put restriction on one or more of the indications, the benefit criteria (cure) could, for at least the indication CAP, be split up in cure - general population and cure - high antibiotic resistance population.

5 Discussion

5.1 Methodology

5.1.1 Appropriate frame

The benefit risk approaches used are chosen to test methodologies which embrace a large variety of features and accommodate the expertise of the case study group, which include previous experience with BRAT, MCDA, SMAA, SPM and SBRAM. All benefit risk analysis on Ketek versus comparators was made with the perspective of the regulatory agencies, at a time point where the market authorisation after 6 year was re-evaluated, and indication restricted.

All approaches only compared two alternatives, Ketek and comparators, where comparator consists of different antibiotics approved for the concerned indication. This approach is chosen due to the summary state of the data in the EPAR, where all safety data are pooled across different comparators.

Generally all methodologies had difficulties supporting decisions regarding restrictions to the indications. A reason for this problem is the summary state of the data.

Generally the limitations of the approaches when choosing benefit and risk criteria are connected to the problem of double counting. This is, especially the case for risk criteria, where a choice had to be made either to list criteria by organs AEs or the seriousness or include both and then try to take the risk of double counting into account in the analysis. Benefit criteria was for most approaches and indication reduced to one “cure rate”, and data from several studies for each indication was available to support this criteria. For the BRAT, MCDA and SBRAM approaches there was a discussion whether to define a cure criterion for each study in order to accommodate the multiple sources of evidence or to sum up through meta-analysis beforehand. For all methodologies the later was chosen.

Table 3: Assessment of appropriate frame for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
BRAT	The BRAT Framework and pilot software provide guidance and a value tree tool for users to select and define benefits and risks. The framework and software are intended to be accessible to project teams that want to frame the benefit / risk assessment on their own or preferably at first with the help of a facilitator. Implementation only requires access to Excel and, during the pilot phase, registration with PhRMA to gain access to the software application and guidance document. The software is user-friendly, with minimal technical demand. Time demands would depend upon the complexity of the problem and availability of data. In this case, the information was already in the EPAR, and framing was done for all methods at once. In a more typical prospective analysis, the framing is often helped by an analyst working with the team to define benefits and risks for the indication of interest.	The software will be turned over to a vendor after the pilot stage, with improvements to be made based on user feedback. For this case study, the framework and tool were applied easily. The software does not calculate the results it displays, so the calculation of combined efficacy and the confidence intervals needed for efficacy and safety variables had to be done outside the tool. Given the complexities of combining data from different studies, this is not recommended to become an automated function.

	BRAT can be used at any stage of the product lifecycle. The software tool is designed to be a data archive if desired, and so can be used early in development and updated throughout the product lifecycle. The pilot software is designed to look at one treatment v. one comparator (active or placebo) at a time for dichotomous variables.	
MCDA	MCDA is a natural progression of PrOACT, it divides difficult problems into manageable smaller criteria so to compare between alternatives. MCDA methodology also allows addition of information easily, when more data become available. MCDA methodology framework is broad and we need to clear in our mind that there are many adaptions to this framework, and we have only tested one adaption using HiView3. Many critiques in this report are based on appraisal of the programme. Software we used in this exercise, HiView3, was easy to use and made the MCDA analysis much efficient. Comparing between alternatives is apparent in both visual and number output with current programme. The HiView3 MCDA model requires criteria values and weights to be precisely known upfront. A detailed decision conference between stake holders is needed to discuss an agreed criteria function in each criteria and precise weight between each criterion; One would imagine it is often difficult and unrealistic to obtain an exact weighting score in real life situation, particularly when number of criteria for consideration is large. Besides, the decision maker's knowledge regarding to the question might not be sufficient to make an objective judgement in weighting. The result weighting and utility scale would be bias towards the stakeholder's own experience or possibility influenced by other participants.	1] Stake holders selected for the decision conference needed to be wide enough to accommodate views from different parties – regulators, physicians & patients 2] Information on criteria would need to be available for review prior to meeting. 3] Question regarding to criteria should be addressed by individuals independent to the decision conference.
SMAA	This case study assumes regulator's perspective to review a drug decision with the data available 5 year after market approval. SMAA is chosen because it has the flexibility in number and form of criteria; it allows the discrepancies and variations in different datasets taken into analysis; it also allows stakeholders to have different opinions on trade-off between criteria. All of these features make SMAA a choice in dealing with real world medical decision problems where uncertainty is almost inevitable. SMAA can be realised by software 'jsmaa'.	The 'jsmaa' may still need further development to include nonlinear utility choices.
SPM using BRR	PSM is applicable to all decision problems to which benefit-risk ratio (BRR) is calculated. It provides the necessary visualization	

	and representation of benefit and risk information and incorporates uncertainty into analysis. The PSM – including the MCS allows uncertainties in the input values, characterised by probability distributions, to be propagated through the network of evidence to the end results. In health care settings, the decision maker is faced with having to make value- or preference-based treatment decisions under uncertainty. Both the risk-benefit joint distribution plot and acceptability curves helps decision maker to trade-off risk and benefit The approach is based soundly on probability theory, is comprehensive in the scope of inputs, provides readily interpretable results, and can be implemented using existing software, such as @Risk or Crystal Ball sitting in Excel, or Analytica, SAS, R or SPLUS. Its outputs are clear, graphical and easy to understand. Approach can display two-dimensional probability distributions for the differences between a new drug and a placebo or a comparator for either measures of favourable or unfavourable effects, or the two combined. For the approach SPM using BRR as metric indices, benefit and risk criteria are limited to one benefit and one risk criteria. In the analysis of Ketek indication ABS this risk criteria as defined by overall incidence of adverse event of special interest (AESI), which were comprised by the sum of hepatic AEs, Cardiac AEs, Syncope and Visual AEs.	
SBRAM	The framework of the Sarac Benefit-Risk Method if easy to follow and clearly described in the material available on e-room PROTECT WP5. However, the process of scoring criteria is not straightforward for layman,and there exists no finished software for the methods. Yet, with some statistical and computational knowledge scoring of criteria can be done using mathematical programs, such as MATLAB with statistics toolbox. For the Ketek analysis, scoring was done using MATLAB and since all parameters were discrete, only one scoring method had to be implemented to produce the different scoring charts.	

5.1.2 Meaningful reliable information

For all approaches used in this case study benefit criteria was cure, which is also primary efficacy endpoint for most studies referred to in the EPAR.

Generally, for all methodologies, considerations were made before deciding on how to use available data due to its summary state. For all methodologies it was decided to pool efficacy data both phase III and phase IV data through meta-analysis except for Sarac's Benefit-Risk Assessment Methodology where data were pooled directly. Safety data from phase III and phase IV studies were pooled for the analysis.

In relation to the original decision by EMA to restrict the indication for Ketek (i.e. concerns regarding QTc prolongation) however, events relating to this is not given explicitly in the report and therefore cannot be taken into account.

The EPAR does not contain direct information on clinical judgment, and the restrictions recommended seems to be based on information from post-marketing safety data reporting exacerbations of myasthenia gravis including fatal cases, several hepatic events and imbalance in incidences of visual disturbance and cases of syncope associating telithromycin/Ketek with increased risks compared to conventional macrolides and beta-lactam agents. However, the post-market surveillance data is not directly reflected in the data presented in EPAR. (Also relevant in connection to discussion on how to make decision on restriction, and the use of data and choice of criteria e.g. post market indication of increased risk).

The ability of the BR approaches to deal with criteria other than efficacy and safety was not tested in this case study.

Table 4: Assessment of using meaningful reliable information for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
BRAT	The same benefit and risk criteria were used for all methods, but BRAT allows the user to define benefit and risk, whether as direct efficacy and safety variables or as other measures or combinations of measures. The inclusion of clinical judgment and patient perspective is not limited by the tool. In fact, variables of interest to different audiences can be displayed or hidden, and there are filters that could be used to display the data from different perspectives, or to display results from observational data v. clinical trial data, for example.	Variables can be rank ordered in the BRAT software. Weighting for different audiences, or levels of severity, for example needs to be done outside the BRAT software, although a team has been looking at the feasibility of incorporating weighting in the tool after the pilot.
MCDA	All benefit and risk criteria listed in the EPAR were used in the MCDA model. Data source were reliable. However, transformation of data to utility score could be bias. As well as the final average weighted score. Both utility function and weighting were set based on stake holder's preference after decision conference meeting – which itself undoubtedly varies. Besides, this HiView3 MCDA software only allows one value for every alternative in each criterion. However, medical data are often in range of mean with confidence interval so to account for the uncertainties and random error with the statistical estimates. The current software would not able to take the uncertainty with data into account, this is crucial in making medical judgements especially in rare events where there is a intrinsically considerable degree of uncertainty with the statistics estimates.	[1] Results range should be used in the model instead of one summary statistic value. Current programme we used in MCDA is not feasible for this type of input
SMAA	The rational for including or excluding criteria are not clearly defined. For example the total AEs and AEs by body system, if all of them are taken as risk criteria, each AE is actually counted twice. Should the weights be adjusted on criteria which are overlapping? In the current SMAA analysis only AEs by body system is included. All data available to decision maker can be taken into analysis by SMAA, high quality or low quality, clinical trial data or observational data. Since SMAA describe performances by distributions, all the data can contribute to distribution	For utility and weight elicitation, should some standard techniques with language understandable to common people be introduced or developed in addition to decision conference?

	estimation (at least in principle) in an accumulative way. As in MCDA, SMAA assigns utility and weight for each criterion. These need both clinical judgements and stakeholders' opinions. SMAA relax the requirement for weights to be exact. The weights can be in a range or totally missing while SMAA still provides answers to help decision makers.	
SPM using BRR	Potential problems in applying the techniques include collapsing benefits and risks into single measures (i.e. BRR). It is unclear how one might incorporate multiple dimensions of risks and benefits. The approach is suitable for two therapies for a binary measure of benefit and a binary measure of risk. However, additional risk and benefit criteria can also be accommodated (ref) in some situations. In this case, multiple thresholds are used to ensure the comparability of all units of benefits and risks.	Bayesian methods can easily be generalized to allow for other distributions of benefit and risk, provided one can simulate samples from the posterior distribution of interest. The Bayesian methods also allow prior information to be incorporated into the inference if such information is available.
SBRAM	Efficacy data were, as mentioned above, pooled directly for the Sarac Benefit-Risk Method approach. This was done because the information material on Sarac's Benefit-Risk Assessment Methodology, as of now, only include a description of scoring discrete variables using trial population size, N, and number of events, x, as input. With the Sarac Benefit-Risk method the clinical relevance of a difference in performance for drug versus comparator for each criterion is defined through the scoring method. This is done through the threshold of 2/3 of the patients performing better for drug versus comparator or vice versa. The threshold of 2/3 can be changed to another level, though this has to be done upfront. However the scoring method does not take in to account the magnitude of an effect of a drug on a criterion.	This limitation in connection to scoring of discrete data, with input N and x could be overcome by developing an additional scoring method, which can still be based on the same principles of $P(X_{Drug} > X_{Comparator}) \geq \alpha$, $\alpha = 2/3$. An approximation to the principle of scoring could be developed with uses the probability, p of an event for drug and comparator and the confidence interval for the probabilities.

5.1.3 Clear values and trade-offs

An area where the approaches chosen are very different is with regard to value judgment. While MCDA and SMAA approaches incorporate explicit value judgment in the model, BRAT & BRR does not include any value judgment. BRR using SPM include value judgment by offering the possibility to determine the probability that ketek is net-beneficial relative to comparator at different risk benefit acceptability thresholds. In the SBRAM methodology the relevance of an effect is determined in an objective manner, by the threshold for which a drug performs better than the other drug on a criterion.

Table 5 Assessment of the availability of clear values and trade-offs for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
BRAT	Value judgments can be displayed through rank ordering of variables, or through inclusion and exclusion of variables. Weighting can be done outside the BRAT software and the weighted data can be displayed with the BRAT tools. Favourable and unfavourable effects are defined clearly based upon the initial definitions included in the value tree. A common scale of proportions is used in the current software, which will display either risk difference or relative risk. The denominator (e.g.,	If one is trying to make direct trade-offs, the approach will facilitate the discussion. The judgment regarding the balance between the factors being traded will still have to be made by the user, but this has been the stated preference of many decision makers, rather than being handed "a number."

	events per 100 or 1,000 or 10,000 patients) is selected by the user. Final results display events of interest side by side, not combined into one metric.	
MCDA	MCDA method allows a transparent judgement of value between risk and benefit. By transforming data into utility score using criteria function, this produce a common scale to allow comparison between risk and benefit Final results are easily interpretable in both graphical and numerical form using the HiView3 software.	
SMAA	By converting performance on each criterion into preference level and assessing the importance of different criteria, different criteria (benefits, risks) are directly comparable. The value judgement is through utility elicitation from stakeholders and decision conference. The results are about overall preferences (satisfactions) for all alternatives. Decision is clear from results.	
SPM using BRR	Both the risk-benefit joint distribution plot and acceptability curves helps decision maker to trade-off risk and benefit	
SBRAM	The Sarac's Benefit-Risk Assessment Methodology approach does not make judgment of values explicit, Sarac's Benefit-Risk Assessment Methodology the drugs are scored in a objective manner by the threshold for which a drug performs better than the other drug on a criterion. The decisions makers has to make judgment about the direction of a criteria, e.g. if more events are good or bad or if an increase of a variable is good or bad. But to which extent an increase/decrease will result in one option being judged better on a criterion or not, is based on an objective scoring Favourable and unfavourable effects are clearly defined in the Sarac Benefit-Risk Method approach. This is an attempt to define clinical significance and an opportunity to investigate and discuss the clinical relevance of data. With the Sarac's Benefit-Risk Assessment approach it is determined if there is a tendency towards the drug performing better or worse than the comparator for each benefit and risk criteria. This is done through the scoring of criteria, and if the drug is judged to have a favourable effect compared to the comparator this means that 2/3 of the patients in the drug group perform better than the comparator for the specific criteria, the drug I found to do worse 2/3 of the comparator patients perform better than the drug patients. If none of either of these thresholds can be fulfilled then the method can not say if there is a difference of the effect for between drug and comparator on the criteria in question. The value of 2/3 can be changed if deemed appropriate. Although it is clearly defined if there is a favourable or unfavourable effect of the drug compared to comparator the method does no tell how big this effect is. The method does not give a direct measure which trade-off of benefits and risks. The result of the analysis is presented visually and gives a clear overview on whether the drug has favourable or unfavourable effect compared to the comparator for each criterion. The method require that weights are assigned to each criterion for the process of scoring is begun, this helps when the final conclusion on the drugs benefit risk profile has to be made,	

	since it has been judged where an effect favourable or unfavourable is considered more of less important compared to other criteria.	

5.1.4 Logically correct reasoning

Table 6: Assessment of the logically correct reasoning for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
BRAT	This approach can handle qualitative or quantitative, objective or subjective discrete data. Uncertainty is shown with confidence intervals. How to combine effects is not dictated by the approach. Correct reasoning and interpretation should be used in choosing to display relative risk or absolute risk, in the same manner that would be used outside this specific application.	Continuous data has to be made dichotomous. Wide variability, i.e., a long bar in the forest plot, can tend to overemphasize a less important variable if the data are not weighted.
MCDA	Each criterion can only hold one value, however in any form. However, uncertainties within the data range are not addressed as this HiView3 MCDA software only allows one value for each criterion. Whereas medical data are not distinct. We used random effect meta-analysis to combine results from different studies listed in our data source. This allows an objective approach to pooled data between studies before using the result in the MCDA model. As discussed earlier, results of the HiView3 MCDA is dependent on precise weight information collected from stakeholders. And these often change dependent on the stakeholder involved and possibility not replicable with different stakeholder groups. As a result, conclusion from each analysis is conditional to the precise weighting decided by the stake holding group. It is arguable if the result is applicable to the wider public.	We would recommend using meta-analysis to combine results from different studies for assessment.
SMAA	SMAA is an extension of MCDA. So it fits for any number and any forms of criteria as MCDA does. SMAA includes uncertainty in performances and uncertainty in choices of weights into consideration. The major concerns behind this extension are (i) the performance of an alternative may change each time new data arrives, so it is suitable to view the performance as a distribution rather than a fixed value. (ii) the choices of weights are hardly agreed exactly in practices. A range for weights or a distribution for weight vector is more realistic in real situations. Under those uncertaintys, SMAA considers the chance (probability) that an alternative is the best one for each alternative as the evidence. SMAA is realised by simulation means. MCDA and SMAA use additive utility function as value function, which implies preference independence and incurs criticism.	The performances of an alternative on different criteria are likely to be correlated. Currently they are taken as independent in SMAA simulations.
SPM using BRR	PSM is applicable to all decision problems to which benefit-risk ratio (BRR) is calculated. It provides the necessary visualization and representation of benefit and risk information and incorporates uncertainty into analysis. The Both the risk-benefit joint distribution plot and acceptability curves helps decision maker to trade-off risk and benefit	

	The approach is based soundly on probability theory, is comprehensive in the scope of inputs, provides readily interpretable results, and can be implemented using existing software, such as @Risk or Crystal Ball sitting in Excel, or Analytica, SAS, R or SPLUS. Its outputs are clear, graphical and easy to understand. The approach can display two-dimensional probability distributions for the differences between a new drug and a placebo or a comparator for either measures of favourable or unfavourable effects, or the two combined.	
SBRAM	Variation in data is considered through the scoring method. The Sarac's Benefit-Risk Assessment Methodology does not offer any additional objective data driven method to deal with uncertainty for discrete data, but offer the possibility of assigning interval scores when subjective judge relevant. However, through re-sampling, it possible to evaluate uncertainty in a data driven way, which can be reflected through an interval score. In the Sarac's Benefit-Risk Assessment Methodology approach benefits and risks are not integrated, all benefit and risk criteria a weighted prior to scoring. The criteria are weighted into one of tree categories; most important criteria, medium important criteria and low importance criteria. All criteria have to be mutual preference independent.	

5.1.5 Commitment to action

Table 7: Assessment of the commitment to action for benefit-risk approaches through practical experience

	Comments	Proposed improvements and/or extensions
BRAT	The approach's value tree facilitated discussion. The visuals were easy to understand. The final results are easily communicable, transparent and easily understood. They are designed for export into PowerPoint for ease of display and communication. The software tool is designed to provide a clear audit trail so that all aspects of the benefit-risk evaluation can be traced	
MCDA	MCDA method divides a complex problem into smaller criteria for assessment, this approach lead the decision makers to develop a deeper insight into the problem to be addressed as well as the alternatives to be considered. Final results from the HiView3 MCDA software are displayed clearly in both numeric and graphical form. Graphical presentation of the results is clear and easy to comprehend. The results are stable and replicable, as long as auditor have the same data, identical utility function and exact precise weight used in the original model. MCDA is a very useful and transparent methodology into decision-making. There are many adaptations into this methodology framework and we have only tested this method using HiView3 software. The software was easy to use and result outputs are clear. However, it is not without limitations. Firstly, each criterion can only take one data at one time. Medical data are presented as an average with a range to describe the underlying uncertainties with the statistics. It would be inappropriate to ignore this issue, especially in cases with rare events which the estimates often associate with a large uncertainty. Secondly, this method requires precise weighting and utility function from decision makers up front. This is often unrealistic and difficult to obtain in real life, particularly when the number of criteria is large. Lastly, result from this HiView3 MCDA approach is conditional to the explicit weighting and utility function set by selected decision makers. This raises the question if the results can be applied in the wider population. This HiView3 MCDA approach allows decision maker to structure the problem and assess the alternatives objectively but it does have a few technical issues that makes it less suitable in medical decisions. MCDA framework is sound and allows stakeholders to make decision in a more transparent and objective approach. There are may adaptations to the MCDA framework, the HiView3 MCDA approach does have a few crucial limitations when applied to medical data.	One major benefit of current MCDA software is that the results are clear and easy to comprehend. This is most useful when used to communicate with other users. We ought to extend this concise and simple minimalistic output to future reporting.

	On balance, the alternative MCDA approach using SMAA is more favourable as the SMAA approach is able to address the limitations associated with medical data.	
SMAA	With summary data from many sources, SMAA is a combination of Bayesian statistics, MCDA and simulation. The results directly lead to the decision to be taken. MCDA plus simulation is a better way to describe SMAA for communication. SMAA deserves to be taken forward since it extends MCDA towards more realistic decision making.	
SPM using BRR	The approach is based soundly on probability theory, is comprehensive in the scope of inputs, provides readily interpretable results, and can be implemented using existing software, such as @Risk or Crystal Ball sitting in Excel, or Analytica, SAS, R or SPLUS. Its outputs are clear, graphical and easy to understand. Approach can display two-dimensional probability distributions for the differences between a new drug and a placebo or a comparator for either measures of favourable or unfavourable effects, or the two combined.	
SBRAM	The final result of the Sarac's Benefit-Risk Assessment Methodology analysis provides an visual overview on whether the drug performs better or worse that comparator, for each of the criteria judged relevant in context of the given decision problem. The Sarac's Benefit-Risk Assessment Methodology stepwise framework helps to structure the decision problem, discuss criteria relevant for the decision and there relative importance. The framework also provides a clear audit trail for the benefit risk evaluation.	

5.2 The assessment of benefit-risk balance

5.2.1 Benefit-risk of Ketek versus comparators

For all approaches the benefit risk assessment was done per indication.

5.2.1.1 Acute Exacerbation of chronic bronchitis (AECB)

The analysis of benefit-risk for Ketek versus a group of comparators for the indication AECB using BRAT gives an overall impression that the benefit risk profile for Ketek is similar to the group of comparators.

Overall the analysis of Ketek versus a group of comparators using MCDA shows that Ketek is more preferable choice by a small margin. Furthermore the sensitivity analysis showed that the balance towards preference of Ketek was not sensitive to changes in weighting of criteria.

Analysing the benefit-risk profile of Ketek versus comparators in the indication AECB using SMAA shows that the benefit-risk balance for Ketek is worse that comparators.

The benefit risk balance of Ketek compared to comparators for the AECB indication using SBRAM is considered to be negative. However considering the data on penicillin or erythromycin resistant S peneumoniae data from a phase IV study, the balance of Ketek can be considered positive in high resistance regions compared to Azithromycin.

5.2.1.2 Community-acquired pneumonia(CAP)

The benefit risk assessment using BRAT for CAP indication shows Ketek has a similar benefit-risk balance as comparators, maybe with a small tendency towards favouring of comparators due to high number of visual AEs for Ketek.

The overall benefit-risk balance of Ketek in the indication CAP using MCDA approach showed comparator was more preferable although only by a small margin. Sensitivity analysis showed the result was easily influenced by the weightings assigned.

The benefit-risk profile of ketek versus comparators in the indication CAP using SMAA shows the benefit risk balance for Ketek is better than that of the comparators. This is still the case after sensitivity analysis by means of missing weights

With the use of SBRAM the overall benefit risk balance of Ketek versus comparators in the indiciation CAP is found to be positive.

5.2.1.3 Acute bacterial Sinusitis (ABS)

BRAT assessment of Ketek benefit risk balance compared to comparators in the indication ABS shows a favourable profile towards Ketek, due to increased cure rate for ketek compared to the group of comparators.

Overall results using MCDA for the assessment of ketek benefit-risk balance versus comparators in the indication showed a small tendency towards preference for ketek. The result was not easily affected by weightings assigned.

The benefit risk assessment of ketek versus comparators using SMAA, shows that ketek is preferable over comparators, however sensitivity analysis showed that this result could be influenced by increasing weights on hepatic and visual AEs.

SPM using BRR shows that there are high probability of Ketek being net-beneficial relative to comparator in the indication ABS for an acceptability threshold of 1 (Preference such that one is willing to accept one event of AESI (adverse event of special interests) to prevent one event of ABS).

Overall benefit risk balance for Ketek versus comparator in indication ABS is not considered to be positive using the SBRAM approach.

5.2.1.4 Tonsillitis/pharyngitis (TP)

The benefit risk profile for Ketek versus comparator in the indication TP using BRAT is judged to give similar benefit risk balance.

Benefit risk balance of Ketek versus comparator in the indication TP using MCDA showed comparator was more preferable by a small margin. This result however could easily be changed by change in weightings assigned to visual and hepatic events.

Benefit risk balance using SMAA approach shows that the benefit risk balance for Ketek versus comparator in the indication TP negative. Sensitivity analysis shows that increasing the weights on hepatic AEs will result in a compatible benefit risk balance for Ketek and comparator.

With the SBRAM approach it is found that the benefit risk profile of Ketek is compatible to comparators in the indication TP.

5.3 Visual representation of benefit-risk assessment results

BRAT

The BRAT method evaluate the consequence for each criterion through summary statistics which is presented in a key benefit risk summary table (KBRS). For some types of tabular outputs, such as odds ratios, it is recommended they are to be presented together with absolute risk, incidence rate or similar. The performance and difference of drug versus comparator for each criterion is also presented in a forest plot which gives an easy overview of risk and benefits between drug and comparator.

In the Ketek case the KBRS table output was displayed as risk difference per 1000 persons for Ketek versus comparator with 95% CI, especially the visual presentation in the forest plot gives a nice overview on the consequences for each criterion.

MCDA

There are several visuals available in the HiView software. The average weighted utility score are clearly visualised in an added value bar graph using HiView3. With green bars indicating benefit and red bar indicate risk. It is also possible to display the added value given for each criterion. The difference between two options is displayed numerically and by bars in a "Difference" display. The software also offers the possibility to produce a graph for the investigation of sensitivity in weights for each node and criteria.

SMAA

The only available software to perform SMAA is jsmaa. In jsmaa, the utility function is always linear with a fixed way to determine the least preferred value and most preferred value (somewhat resembles the relative option in Hiview); the choices of weights can be exact, in range, or missing. The distributions that user can use to describe the criteria performances include Gaussian, uniform (interval), beta, lognormal etc. Certainly, exact value is allowed in case that there is no certainty. In case that a user has no idea on weights, jsmaa can help to summarize all weights and classify them into categories according to the alternatives they are favouring.

BRR using PSM

PSM is applicable to all decision problems to which benefit-risk ratio (BRR) is calculated. It provides the necessary visualization and representation of benefit and risk information and incorporates uncertainty into analysis. Both the risk-benefit joint distribution plot (an array and visualization of the simulated joint density of incremental risks and benefits illustrated on an x–y scatterplot) with ellipse confidence interval) and acceptability curves help assess the uncertainty around the risks and benefits. The approach is based soundly on probability theory and can be implemented using existing software, such as @Risk or Crystal Ball sitting in Excel, or Analytica, SAS, R or SPLUS. Its outputs are clear, graphical and easy to understand.

SBRAM

The results of the benefit risk analysis is displayed in a scoring table where the score +1 on a criteria means that the drug is considered to perform better than comparator, -1 that the drug is considered to perform worse that comparator and zero that neither can be stated. These results is displayed visually in a tornado like diagram, where the score for each criteria is shown by a colour (green - score +1, red - score -1 and yellow - score 0) and by the placement of the colour bar, to the right from the centre of the diagram for score +1, to the left of the centre for score -1, and for score zero in the centre. The visual presentation gives a nice overview of data and the performance of the drug in relation to comparator.

6 Conclusion

This is a simple case study and it would be inappropriate to recommend one single methodology from our experience without testing finer difference between these methodologies with more complex cases. Instead, we will give some recommendations for further research in wave 2.

The case study was prepared using the PrOACT-URL framework, and all benefit-risk methodologies tested could be used with in this framework to aid the decision process. The comprehensive benefit risk approaches, BRAT, MCDA, SMAA and SBRAM all include a structured stepwise process with many similarities to PrOACT-URL. In the following the five quantitative benefit risk approaches will be assessed in relation to the steps of the PrOACT-URL framework.

6.1.1 Problem

This step is part of the definition of decision context within BRAT, MCDA, SMAA and SBRAM

We found this step to be as crucial as the decisions process. We would recommend that the process of framing the problem is done carefully in order to decide which quantitative benefit risk methodology to be use in benefit risk analysis.

6.1.2 Objective

There are four indications of Ketek and risk-benefit assessment in this case study was considered separately. Each assessment includes one benefit criteria and several risk criteria.

There are no limitations with regards to the number of benefit and risk criteria in BRAT, MCDA (SMAA) and SBRAM. Whereas, the metric indices Benefit Risk Ratio (BBR) is confined to one benefit criteria compared to one risk criteria. As a result, the four risk criteria was summarised into one by summing the number of adverse events [cardiac events, hepatic events, visual events and syncope]. We assumed that the severities were similar between adverse events and there each adverse event was independent, and there were no risk of double-counting.

The BRAT, MCDA and SMAA approaches define the objectives in terms of criteria and structure the criteria in form of a value tree/effect tree. The software used with BRAT (BRAT Framework and Software Tool- Beta3.0) and MCDA (HiView3) have a built in function to help visualize the value tree/effect tree. Criteria defined through the process can also be used in the BRAT and SBRAM.

6.1.3 Alternatives

There are only two alternatives stated in the EPAR - Ketek and standard treatment antibiotics as comparators. The MCDA and SMAA can compare multiple alternatives simultaneously. BRAT, SBRAM and the BRR with PSM can only compare two options at a time, this does not need to limit the use of these methodologies to only two options. Analysis on more than two alternatives can be done comparing by combinations of alternatives, albeit rather cumbersome.

6.1.4 Consequences

All methodologies tested included this step in the decision process apart from the BRR with PSM.

MCDA and SMAA
The consequence for alternatives in each criterion is evaluated using utility score generated by a criterion value function. This information can then be presented in an effects table.

BRAT
The BRAT approach display data through summary statistics. Drug and comparator performance is presented in a Key Benefit Risk Summary Table (KBRS) for each criterion. The KBRS table can be used to present different summary statistics with 95% confidence interval, such as rate difference, odds ratios and NNT NNH.

SBRAM
In the SBRAM, the consequence for drug versus comparator for each criterion is evaluated based on a data driven scoring method which uses descriptive statistics to determine if the drug performs better, worse or nether on a criterion compared to control. The drug is deemed to be better if 2/3 of the patients in the drug group has to perform better that the patients in the comparator on a criteria and vice versa. If neither of the above criteria are fulfilled it can be said if the drug performs neither better or worse than comparator. The 2/3 threshold of can be changed depending on the indication, but this has to be stated upfront in the decision context. The magnitude of an effect (risk or benefit) of a drug in not used directly in the this approach.

There is no commercial software available for scoring of criteria or for producing the tornado-like diagram. The scoring method is described more thoroughly in the manuscript “Balancing benefits and risks – data-driven clinical benefit-risk assessment” Sarac et al. (posted at eroom - WP5/WSB/Contributed materials/Methodology materials). Scoring method for continuous variables and discrete variables are described, however the method for discrete variables uses trial population size , N , and number of events, x , as input.

6.1.5 Trade-offs

BRAT and SBRAM methods does not numerically trade-off benefit and risks. In the SBRAM all criteria are categorised into high importance, medium importance and low importance, in connection to the decision context, and are assigned weights 3, 2 and 1 respectively. The weighting in done before scoring of data and the weight of each criterion is presented both in the scoring table numerically (3, 2 and 1) and in the visual display of results (the tornado like diagram). The weight can aid in the discussion when trying to determine the overall balance between benefit and risk.

In MCDA, the process of balancing benefit and risk are broken down by the process of swing weighting between criteria. This process is to ensure that utility score across all the criteria are exchangeable and can be used in forming trade-offs. Weights for each criteria and utility function are formed with a decision making conference involving stakeholders. Information regarding weights and utility function is required upfront for the model. An average weighted utility score is calculated by summing the weighted utility score on all benefit and risk criteria.

SMAA is in same family as MCDA. Instead of requiring precise weight information from decision makers upfront as representation of trade-offs, this method can estimate probability of each alternative achieving the most preferred option when no weight information are available by exploring different weight combinations using computer simulations. This methodology can also be

used when weight information are presented in range or when only the ranking of criteria are available. Results from the SMAA are presented in a bar chart displaying the probability of the alternatives achieving the most preferable option or the probability achieving the r^{th} rank in r options. Apart from the preference information, the current software [JSMAA] also estimates the hypothetical weight combination on all criteria for each alternative that allows that particular alternative to be the most preferred choice. This can be then used is discussion with stakeholders in decision meetings.

6.1.6 Uncertainty

There are two main issues related to the evaluation of uncertainty in connection with the benefit risk balance; (1) the uncertainty in data and (2) the uncertainty in value function and weights.

The BRAT and the SBRAM uses data directly with no value judgment. Uncertainty around value judgment "weighting" can be done in a qualitative way. Uncertainty in data is taken into account in both approaches, in BRAT through the display of 95%CI and in SBRAM variation in data is used in the scoring method. Furthermore it is possible to assign an interval score based on subjective judgments around data quality.

The MCDA method includes sensitivity testing the result robustness in relation to weighting of criteria. It is suggested to include uncertainty in data by using a range as input to the value function instead one summary statistic value. This is not possible in the current version of HiView. One of advantages of SMAA is that it addresses the limitation of current MCDA by including sampling variation and preference uncertainty in the analysis by using distribution as input for each criterion and using distribution or range value as input for choice of weights.

6.1.7 Linked decisions

The BRAT, MCDA, SMAA and SBRAM all increase transparency in the decision process and with clear audit trail. Therefore they can all add to consistency in further decisions.

6.2 Recommendations

The PrOACT-URL framework supports any benefit risk assessment and provides a structured approach to assess and manage the problem raised. The definition of the decision context is a crucial step in the decision process, so to choose the best quantitative benefit risk assessment approach.

Ketek case study is simple yet useful to test out feasibility of some methodologies but not complex enough to determine the finer differences between each methodology for us to make a definite recommendation. However, this exercise does highlight that different methodology are not all the same. Each has its advantages and disadvantages.

Overall, we feel that the application of methodologies we tested can be divided into 2 groups depending on the purpose of the analysis either to"

1. *summarise data and present to stakeholder for decision making or*
2. *to provide an assessment and/or support of decision made by stakeholder during decision making process by analysing information collected by study data and stakeholder preference*

Group 1:

We would recommend BRAT or SBRAM - if the purpose is to summarise data and present to stakeholder for decision making. The BRAT method presents the performance of two options against each other for each benefit and risk criteria in a key benefit risk summary (KBRS) table.

Advantages:

- Performance between alternatives can be presented as proportions, as rate differences or relative risk with the 95% confidence intervals.
- Apart from numeric presentation in table, data can also be presented visually in a forest plot. The KBRS table with the forest plot together gives an easy overview of performance of two.
-

Disadvantages:

- Information about relative importance between criteria and preference values are not included in the framework.
- The process of trading off between benefits and risks is left to the stakeholder with results presented from this framework.
- This method does require some basic statistics knowledge with stakeholders.
- The current BRAT Tool is limited to dichotomous endpoints on two treatments, although not a limitation to the PhRMA BRAT framework itself.

The SBRAM presents the performance of two options against each other for each criterion visually, in a tornado like diagram. The performance between 2 options in a criteria is determined to be superior, inferior or non-inferior using descriptive statistics. An option is deemed to be superior in a criterion if 2/3 of the patients from this option perform better than the patients from the alternative, and vice versa. The option is considered to be non-inferior if it does not fulfil neither superior nor inferior category.

This method requires weighting of benefit and risk criteria into high, medium and low importance upfront prior to the analysis. The weight assigned to each criterion is displayed in the tornado like diagram.

Advantages:

- The performance and overview of alternatives on each criterion together with the weight of each criterion is easily communicated using the tornado like diagram
- Although the analysis of the performance requires mathematical and statistical skills, the diagram can be interpreted easily by a layman. It is then left to the stakeholder to make a decision on the overall benefit risk balance, based on own judgments, while taking into consideration the pre-assigned criteria weight as a guidance.

Disadvantages:

- This method is limited to comparing two options at a time, if the assessment considers several options the assessment can be done by comparing combinations of options, albeit rather cumbersome.

- Although the boundaries for superiority and inferiority can be adjusted according to stakeholder preference and clinical background, this method removes the actual information regarding performance on each alternative.

Both BRAT and SBRAM can be easily updated, either by additional data on a criterion or by including new criteria. Benefit risk assessment made at different time points can be compared with both methods.

Group 2:

We would recommend MCDA and SMAA if the purpose is to provide an assessment and/or support of decision made by stakeholder during decision making process using study data and stakeholder preferences collected. Both methods require the stakeholder to be involved during the analysis process.

In MCDA, the performance of options in each criterion is evaluated using utility score generated by a criterion value function. This information can then be presented in an effects table. The process of trading-off benefits and risks are broken down by the process of swing weighting between criteria, which insure the utility scores are exchangeable across all criteria. Both weights and utility is assigned explicitly prior to analysis by stakeholders. The final result of MCDA is an overall benefit risk score for each option in the assessment, the higher the value of the overall benefit-risk score the better the alternative performed based on clinical data and stakeholder preferences.

Advantages:

- The results are presented in added value diagram, where the contribution to the benefit risk score for each criterion can be displayed.
- The method also includes several plots to investigate the robustness on the result, in relation to the weighting.
- This method provides an transparent approach to decision making

Disadvantages:

- This method require explicit and precise weight information from stakeholder upfront to the analysis, which is often difficult to obtain in real life.
- Results from this analysis is sensitive to weight information, which often varies between stakeholders.
- The current software tested, HiView3, can only take a single value on each alternatives for each criteria. Medical data often presented with confidence intervals to represent statistical uncertainty and this software is not able to manage this limitation.

SMAA is in same family as MCDA. Instead of requiring precise weight information from decision makers upfront as representation of trade-offs, this method can estimate probability of each alternative achieving the most preferred option when no weight information are available by exploring different weight combinations using computer simulations. This methodology can also be

used when weight information are presented in range or when only the ranking of criteria are available.

Advantages:

- Results from the SMAA are presented in a bar chart displaying the probability of the alternatives achieving the most preferable option or the probability achieving the r^{th} rank in r options.
- Apart from the preference information, the current software [JSMAA] also estimates the hypothetical weight combination on all criteria for each alternative that allows that particular alternative to be the most preferred choice. This can be then used is discussion with stakeholders in decision meetings.

Disadvantages:

- Although specialist skill is not needed to understand the visual and numeric presentation from this methodology, this method does require a sophisticated knowledge with simulation and mathematics to understand the underlying mechanism behind the theory.
- Options of utility function are limited to linear function with the current software, JSMAA. Further work on improving this limitation is being considered

6.3 Recommendation to wave 2 case studies

This case study was simple yet provided our team with an in-depth understanding of the various BR methodologies. However, it was difficult to make a definite recommendation of which methodology to bring forward to Wave 2 based on our experience.

We would recommend:

1] Cases with more than 2 alternatives
2] Cases with pre and post marketing data to assess if methodologies can be adapted to changes in data.

7 References

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8 Appendix

8.1 Timeline

Project task	Persons	start	finish
Task 1: Kick-off Meeting	Team	13-07-11	13-07-11
Task 2: Define Decision context	Team	13-07-11	13-07-11
Task 3: Identify Methods to Apply	Team	13-07-11	13-07-11
Task 4: Task Allocation	Team	13-07-11	13-07-11
Task 5: Extract Data	NW/CH/IAPO rep	02-08-11	15-08-11
Task 6: Initial Value Tree	Team	02-09-11	02-09-11
Task 7: Analysis 1	GL/GQ/EC	03-09-11	31-10-11
Task 8: Analysis 2	GL/GQ/EC	03-09-11	31-10-11
Task 9: Analysis 3	GL/GQ/EC	03-09-11	31-10-11
Task 10: Analysis 4	GL/GQ/EC	03-09-11	31-10-11
Task 11: Report Preparation & Submission	Team	01-11-11	16-12-11

8.2 Team Members

NW= Nan Wang (Imperial); CH=Christine Halgreen (NovoNordisk); GQ=George Quartey (Genentech); GL= Guiyuan Lei (Roche); SH=Steve Hobbiger (GSK); MM=Marilyn Metcalf (GSK); EC=Edmond Chan (Imperial);

8.3 List of figures

8.4 Appendix A: Data on Ketek from EPAR

CAP (Community Acquired Pneumonia)

Efficacy CAP (Community Acquired Pneumonia)

Study		Drug	Treatment	N	n	Comparator	Treatment	N	n	Efficacy parameter
A3001	Phase III, randomised, double-blinde, comparative	Telithromycin	800mg sid, 10 days	149	141	Amoxicillin	1000mg tid, 10 day	152	137	Cure/failure - PPc
A3006	Phase III, randomised, double-blinde, comparative	Telithromycin	800mg sid, 10 days	162	143	Clarithromycin	500mg bid, 10 days	156	138	
A3009*	Phase III, randomised, double-blinde, comparative	Telithromycin	800mg sid, 7-10 days	80	72	Trovafloxacin	200mg sid, 7-10 days	86	81	
A4003	Phase III, randomised, double-blinde, comparative	Telithromycin	800mg sid, 7 days	159	142	Clarithromycin		146	134	
		Telithromycin	800mg sid, 5 days	161	143	Clarithromycin		146	134	
A3000	Phase III, open-lable uncontroled	Telithromycin	800mg sid, 5-7 days	197	183	-	-	-	-	
A3009OL	Phase III, open-lable uncontroled	Telithromycin		187	175	-	-	-	-	
A3010	Phase III, open-lable uncontroled	Telithromycin		357	332	-	-	-	-	
A3012	Phase III, open-lable uncontroled	Telithromycin		723	646	-	-	-	-	
A4015	Phase IV	Telithromycin		242	208	Locally prescribed regimen		240	189	

PPc – per protocol analysis fo post-therapy/toc (test of cure) of clinical outcome

sid – once daily, bid – twice daily, tid – tree times daily

*Study terminated early

Safety - CAP

	N		TEAEs		SAEs		Hepatic adverse events		Cardiac adverse events		Visual adverse events		Syncope	
	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp
Polled data from phase III trials A3001, A3006, A3009, A4003	916	723	484	352	34	38	45	33	4	3	11	4	2	2
Polled data from phase III open -lable	1745	-	65	-	4	-	50	-	1	-	9	-	-	-
Polled data from phase IV trials	404	398	168	179	27	333	12	13	-	-	3	1	0	1

Additional 3 phase IV studies confirmed the high clinical efficacy of telithromycin in CAP with trend for superior efficacy in on study (A4015)

ABS (Acute Bacterial Sinusitis)

Efficacy - ABS

		Drug	Treatment	N	n	Comparator	Treatment	N	n	Efficacy parameter
A3002	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	123	112	telithromycin	800mg sid, 10 days	133	102	Cure/failure - PPc

A3005	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	146	110	Amoxicillin/clavulanic acid	500mg/125 mg tid, 10 days	137	102	Cure/failure - PPc
A3011	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	189	161	Cefuroxime axetil		89	73	Cure/failure - PPc

PPc – per protocol analysis of post-therapy/toc (test of cure) of clinical outcome

sid – once daily, bid – twice daily, tid – tree times daily

*Study terminated early

Safety - ABS

	N		**TEAEs**		**SAEs**		**Hepatic adverse events**		**Cardiac adverse events**		**Visual adverse events**		**Syncope**	
	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp
Polled data from phase III trials	750	366	392	182	7	2	13	2	0	1	9	3	0	1
Polled data from phase III open -label	333	-	114	-	4	-	14	-	2	-	1	-	-	-
Polled data from phase IV trials	565	579	149	145	2	2	0	1	-	-	7	1	0	0

Additional 3 phase IV randomized controlled studies performed in the ABS indication in adults showed that telithromycin was non-inferior to moxifloxacin, high dosage amoxicillin/clavulanic acid (875/125 mg bid) and amoxicillin/clavulanic acid (500/125mg tid). Time to symptom resolution was shown to be similar between telithromycin and moxifloxacin, and shorter with telithromycin than high dose amoxicillin/clavulanic acid (median time 4.0 vs. 5.0 days)

AECB (Acute Exacerbation of chronic bronchitis)

Efficacy - AECB

		Drug	Treatment	N	n	Comparator	Treatment	N	n	Efficacy parameter
A3003	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	115	99	Amoxicillin-clavulanic acid		112	92	Cure/failure - PPc
A3007	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	140	121	Cefuroxime		142	118	Cure/failure - PPc
A3013	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	225	193	Clarithromycin		231	206	Cure/failure - PPc
	Phase IV	Telithromycin	800mg sid for 5 days	177	23	Azithromycin		106	30	PERSp at TOC – mITT population
						Cefuroxime		130	17	

PPc – per protocol analysis fo post-therapy/toc (test of cure) of clinical outcome

sid – once daily, bid – twice daily, tid – tree times daily

*Study terminated early

Safety - AECB

	N		TEAEs		SAEs		Hepatic adverse events		Cardiac adverse events		Visual adverse events		Syncope	
	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp
Polled data from phase III trials	609	626	248	301	13	16	9	12	1	3	1	2	1	0
Polled data from phase IV trials	2132	2802	323	321	32	28	1	0	-	-	9	4	4	1

In addition four controlled Phase IV (on mentioned I table above) studies confirmed the clinical efficacy of telithromycin for the treatment of AECB in Adults.

TP (Tonsillitis/Pharyngitis)

Efficacy - TP

		Drug	Treatment	N	n	Comparator	Treatment	N	n	Efficacy parameter
A3004	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	115	97	Penicillin	500mg tid, 10 days	119	106	Cure/failure - PP
A3008	Phase III – randomised , double-blind, comparative	Telithromycin	800mg sid for 5 days	150	137	Clarithromycin	250mg bid, 10 days	135	119	Cure/failure - PP

PP – per protocol analysis of post-therapy/toc (test of cure) of bacteriological outcome

sid – once daily, bid – twice daily, tid – tree times daily

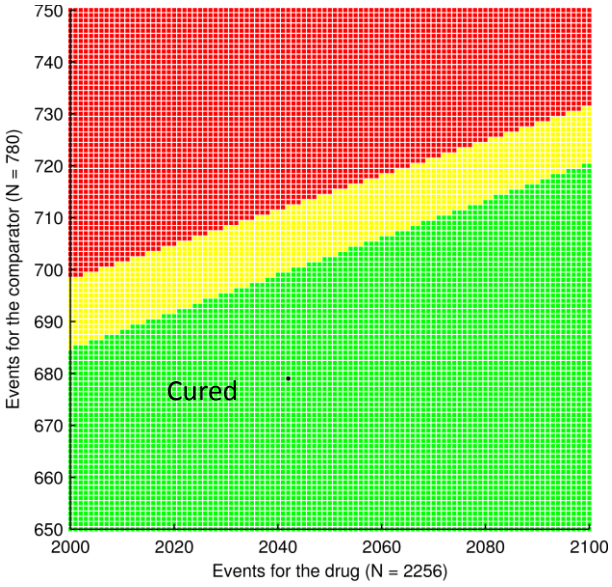
*Study terminated early

Safety - TP

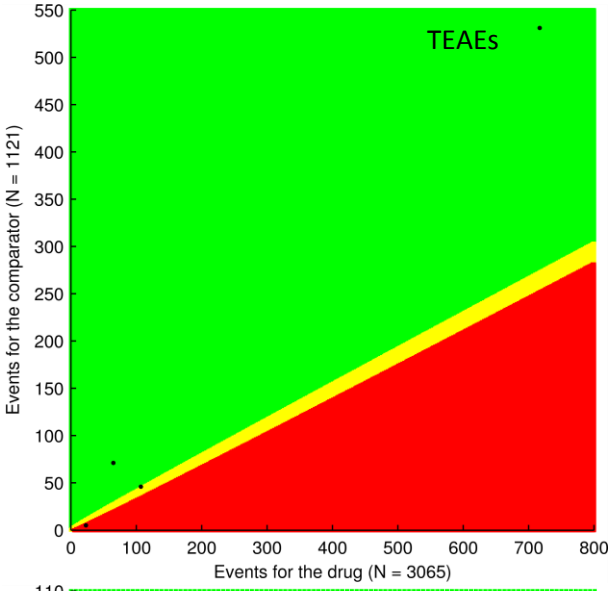
	N		TEAEs		SAEs		Hepatic adverse events		Cardiac adverse events		Visual adverse events		Syncope	
	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp	Drug	Comp
Polled data from phase III trials	427	424	224	200	5	5	7	12	0	0	9	0	0	0

8.5 Sarac's Benefit-Risk Assessment Methodology Appendix B: Scoring Charts

Below scoring chart for CAP, Efficacy, data pooled from phase III comparative and open label and phase IV. For data point in (green area – in favour of drug, red area – in favour of comparator and yellow area, neither in favour)



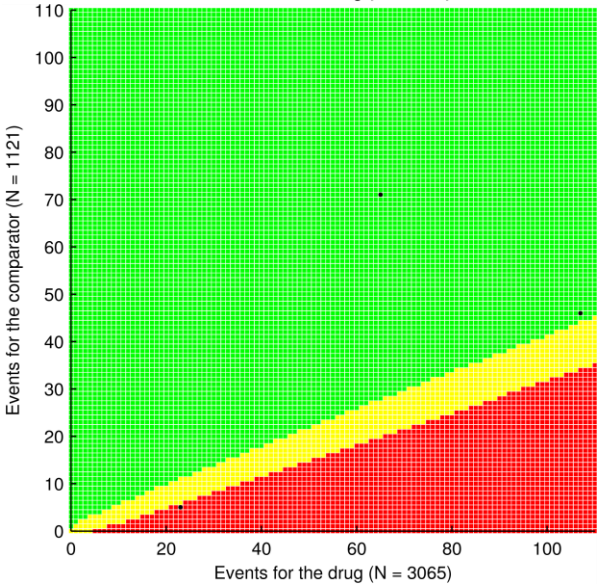
Below scoring chart for CAP - AEs. Data pooled from Phase III comparative and open label and phase IV - the right graph shows the bottom left corner of the left graph.

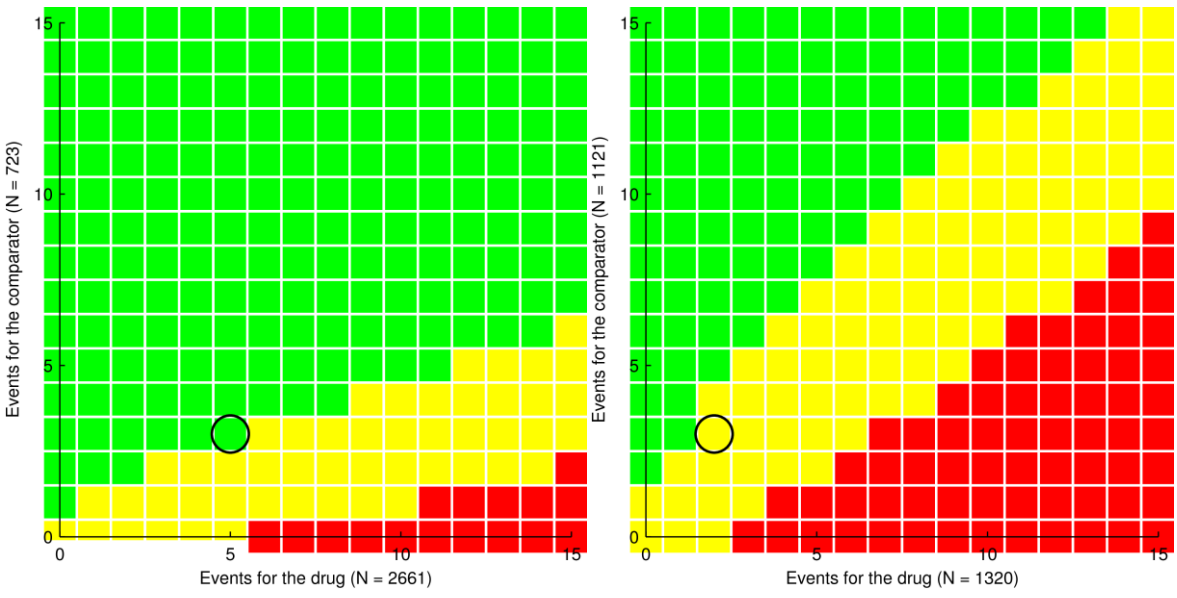


SAEs

Hepatic AEs

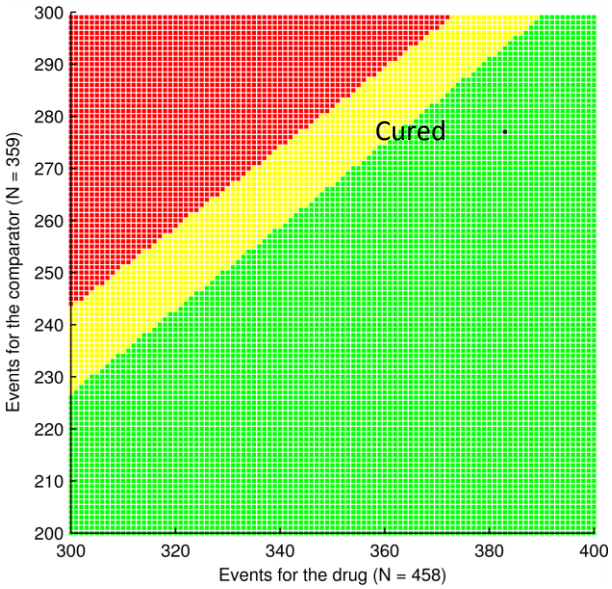
Visual AEs



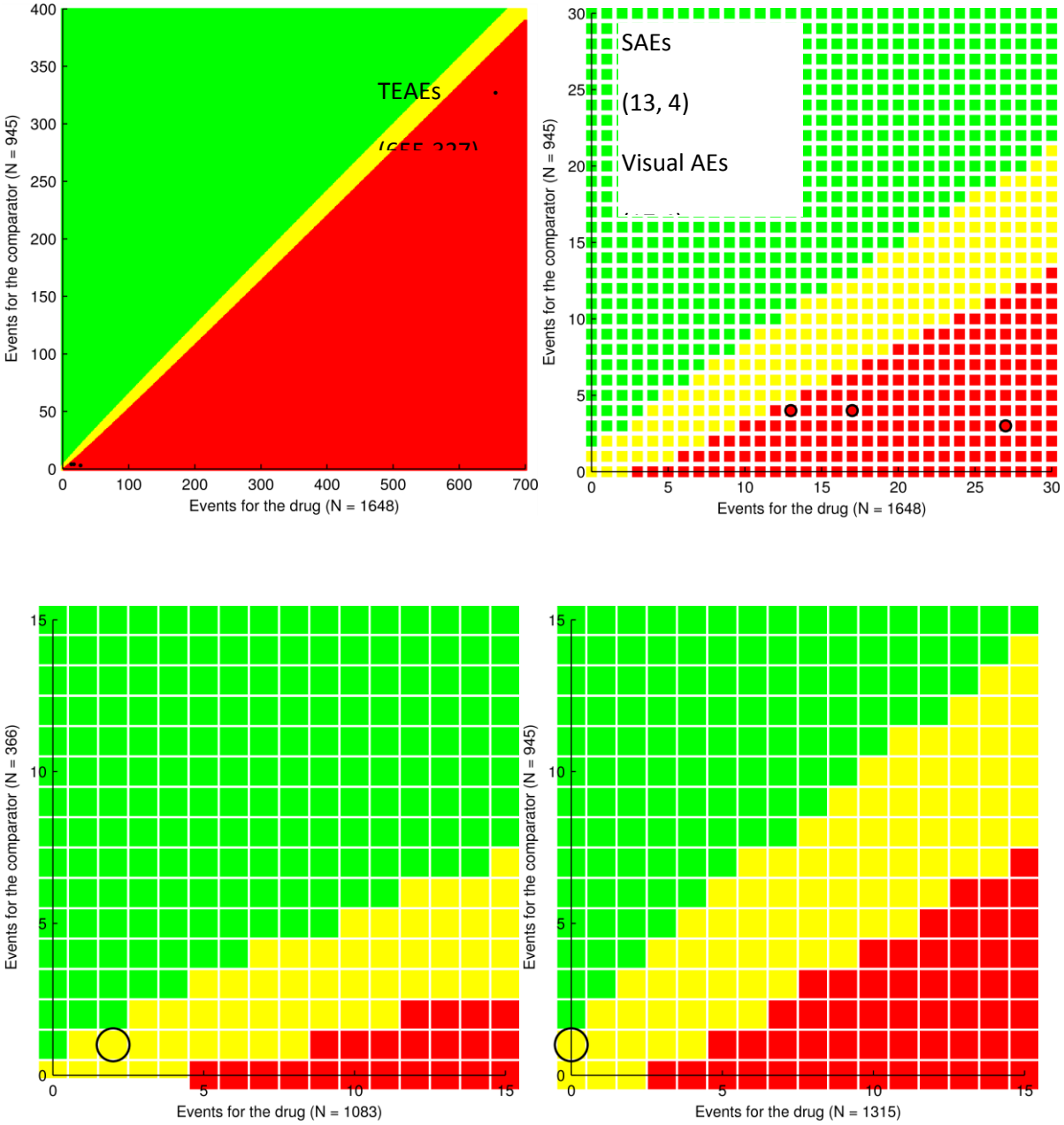


The above scoring charts for CAP - Cardiac AEs, data pooled from phase III comparative and open label studies to the left and Syncope AEs, data pooled from phase III comparative and phase IV studies to the right.

Below are scoring chart for ABS Efficacy criteria. Data pooled from phase III comparative and open label and phase IV, above.

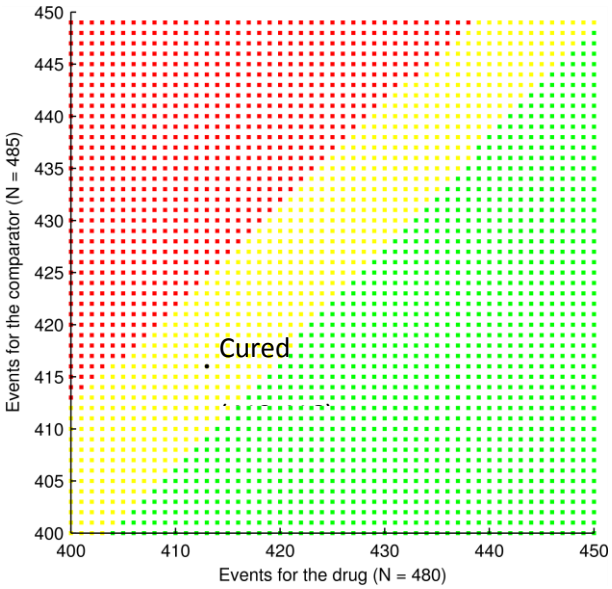


Scoring chart for ABS risk criteria are shown below. Data pooled from Phase III comparative and open label and phase IV, below - the right graph shows the bottom left corner of the left graph

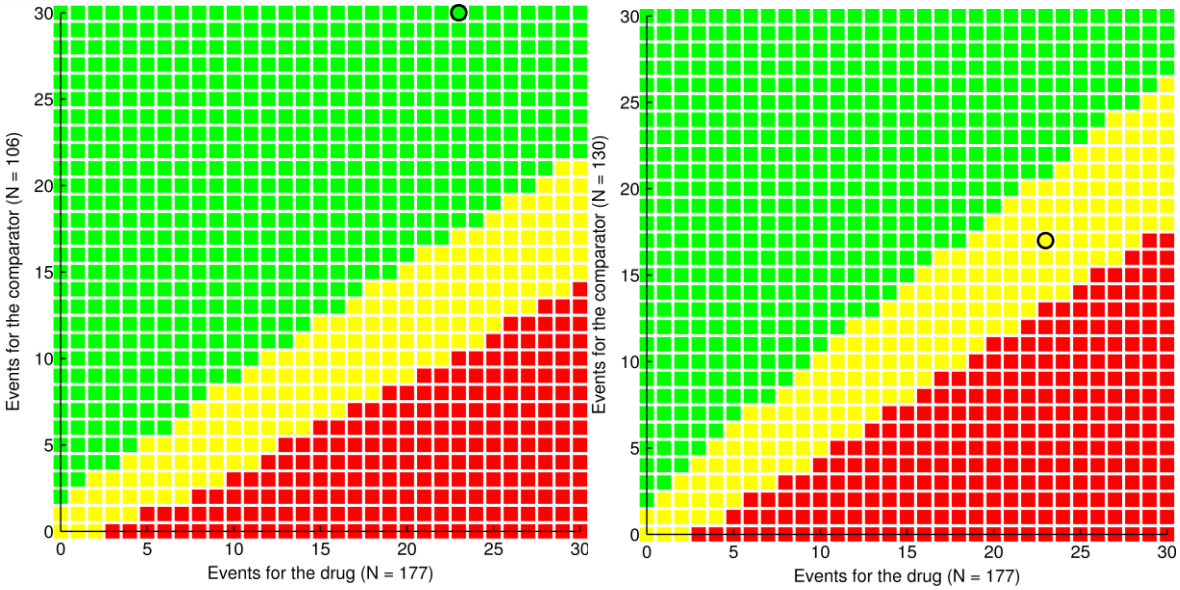


Above plots show scoring chart for risk criteria for ABS, Cardiac AEs to the left and Syncope to the right. Data pooled from phase III comparative and open label studies for Cardiac AEs and pooled from phase III comparative and phase IV studies for syncope.

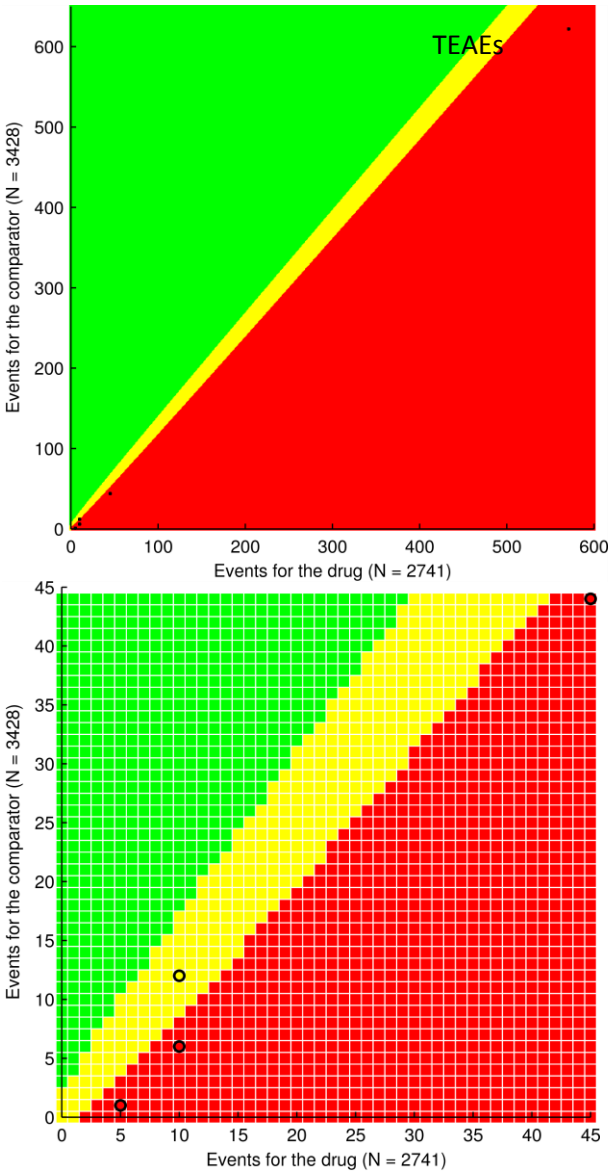
Scoring chart for AECB benefit criteria cure are shown below. Data pooled from phase III comparative and phase IV studies.



Below are scoring Chart AECB, benefit criteria PERSp at TOC for telithromycin vs. Cefuroxime, data from phase IV study (left), and AECB, Efficacy PERSp at TOC for telithromycin vs. Aztihromycin, data from phase IV study (right)



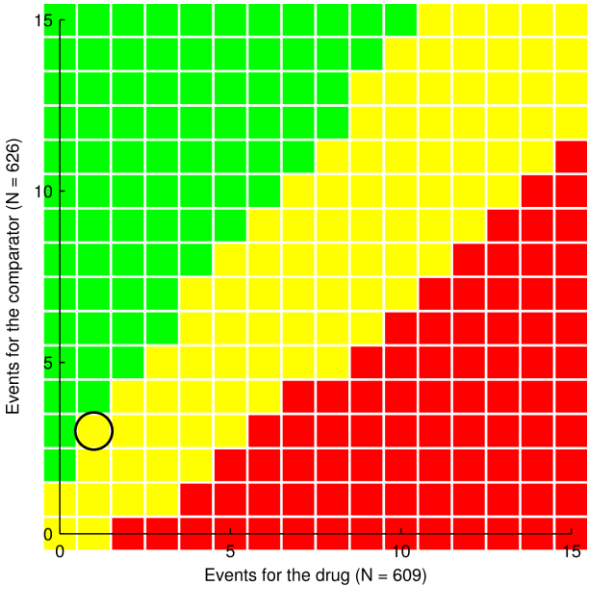
Below to the left are scoring chart for AECB AEs, data pooled from Phase III comparative and phase IV studies - the right graph shows the bottom left corner of the left graph



Hepatic AEs (10, 12)

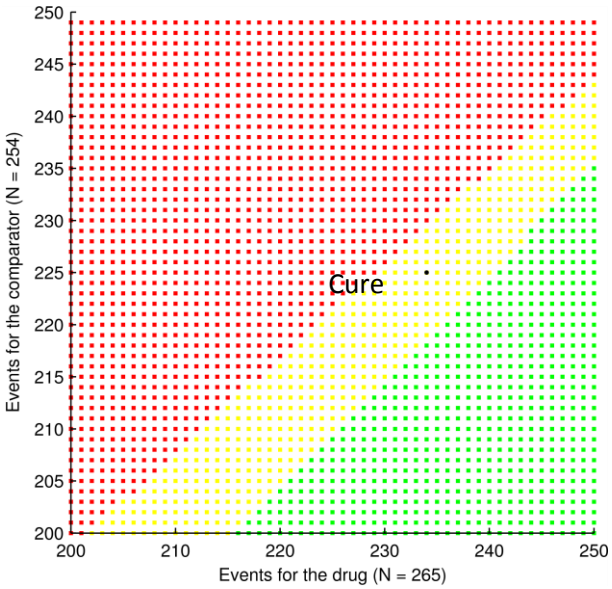
SAEs (45, 44)

Visual AEs (5, 1)



Above Scoring Chart for ABS Cardiac AEs, data pooled from phase III comparative studies.

Below are scoring chart for TP benefit criteria cure, data pooled from phase III comparative studies.



Below scoring chart for TP risk criteria, data pooled from Phase III comparative studies - the right graph shows the bottom left corner of the left graph