Pharmacoepidemiological Research on Outcomes
of Therapeutics by a European ConsorTium

IMI Work Package 5: Supplement 1 to Wave 1 Case Study Report 1:b:iii:

Raptiva® (efalizumab)

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17/06/2013	Shahrul Mt-Isa	Updated trade name to generic, plus other editorial changes.

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1 PrOACT-URL

Case Study Report: Efalizumab (Raptiva®)

as prepared according to the IMI-PROTECT Work Package 5, Work Group D guidelines

This Guideline is based on PROACT-URL, a generic framework for decision making, as explained in Hammond JS, Keeney RL, Raiffa H, *Smart Choices: A Practical Guide to making Better Decisions*, Boston, MA: Harvard Business School Press; 1999.

STEP	DESCRIBE	DATA SOURCES
PrOBLEM 1. Determine the nature of the problem and its context.	**1a. Medicinal product**: The medicinal product is Raptiva (Efalizumab). Marketed biological entity. Is a recombinant, humanized IgG1 monoclonal antibody that targets CD11a, the α-subunit of leucocyte function associated antigen 1 (LFA-1). Mechanism of action may lead to inhibition of leucocyte migration, similarly to natalizumab.	
	1b. Indication(s) for use: Efalizumab is indicated in the treatment of "high need" adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA. The duration of initial therapy is 12 weeks. Therapy may be continued only in patients who responded to treatment (PGA good or better). Together, the clinical pharmacology of efalizumab and the safety and efficacy data (including 2 phase 3 studies with 1.0 mg/kg/week and 2.0 mg/kg/week) support the selection of 1.0 mg/kg/week SC as the optimal dose for efalizumab. (EPAR scientific discussion)	EPAR: EU authorisation on 20th September 2004. Suspended Feb 2009, withdrawn June 2009;
	1c. The therapeutic area and disease epidemiology: Moderate to severe chronic plaque discoid psoriasis. Psoriasis is a common chronic, squamous dermatosis with polygenic inheritance and a fluctuating course. Principal histological findings are Munro microabscesses and spongiform pustules; also seen are rounded, circumscribed, erythematous, dry, scaling patches of various sizes, covered by greyish white or silvery white, umbilicated and lamellar scales, usually on extensor surfaces, nails, scalp, genitalia and the lumbosacral region.	Standard Text Books Raptiva RMP update Nov 2008 pages 30-40
	1d. The unmet medical need: At the time of initial Market Authorisation, there are well established systemic treatments (cyclosporine, methothrexate, PUVA) all of which with serious Adverse Effects	CHMP Opinion EMEA/CHMP/3552/2009;

	(but B-R of the drugs is well established for a long time). At the time of the reevaluation of the B-R of Raptiva (Jan 2009) there are more recent alternative therapies (biologic treatments for moderate to severe psoriasis in "high need" adult patients e.g adalimubab, etanercept, infliximab, ustekinumab. with established efficacy but long term safety still uncertain in the psoriasis indication (although with longer experience in other indications such as RA)	Serono internal data: Serono analysis of patients treated with efalizumab after previous treatment with anti-TNF (26 Jan 2009)
	Severity of condition: Psoriasis is a chronic disease, leading in its severe forms to a significant social disability impacting both professional and social life. Although psoriasis is a serious disease, with potential severe negative impact on the patient's social life, it is not a life-threatening disease apart from rare erythrodermic forms which were excluded from the clinical trials population and was not part of the approved indication (nor were pustular forms of the disease and psoriatic arthritis)	Rapporteurs' Final Assessement Report EMEA/H/C/00542
	Affected population: "high need" adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA **Patient concerns**: impact on quality of life, physical appearance and social functioning **Physician concerns**: chronic and incurable with unpredictable flare ups, interested in long term efficacy	
	Time frame for health outcomes: 12 weeks for PASI 75 (efficacy/favourable effects)), 3 years for PML (safety/unfavourable effects). PASI 75 (primary endpoint) is a 75% reduction of the PASI score at week 12.	Marketing authorisation, pivotal studies
	1e. What is to be decided: Re-evaluation of benefit-risk of efalizumab was prompted by incidence of emerging adverse events in the post-marketing period, i.e. presentation of PML (Progressive Multifocal Leucoencephalopathy) in addition to other serious risks (cardiotoxicity, neurotoxicity, serious infections including tuberculosis). The question to be addressed is: are there in January 2009 any risk minimisation measures which could be rapidly implemented, thus maintaining the B-R balance of the drug as positive? If not, should the Market Authorisation be suspended/revoked?	Efalizumab RMP update Nov 2008 Responses of the Scientific Advisory Group CNS to the CHMP list of questions on Rapitva 7 Jan 2009. EMA/24463/2009
	By whom: the Case study takes the regulator's perspective (1ST step of the efalizumab Task Force); next perspective to be addressed is the psoriasis patient's perspective, given the significant social impact of the sever forms of the disease. **When**: 16th January 2009. Experts believed the margin of benefits over risks had narrowed since approval, i.e. modest efficacy and increased risks. The European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the Committee to assess the above	Scientific Conclusions EMEA/H/C/000542/A20/0028 EMA/CHMP/3552/2009

	concerns and its impact on the benefit/risk balance for efalizumab, and to give its opinion on measures necessary to ensure the safe and effective use of efalizumab and on **whether the marketing authorisation for this product should be maintained, varied, suspended or revoked**. The CHMP also took advice from the Scientific Advisory Group before making a decision. The efalizumab case study intends to reproduce the decision made by the CHMP in February 2009, but using a quantitative model.	
2. Frame the problem.	**2a. Problem of uncertainty, multiple conflicting objectives, combination of the two, or something else?** The 4 PML cases are not strongly confounded. The positive diagnosis is serologically confirmed in 3/4. There are no alternative diagnosis. The uncertainty relates mainly on the relationship between duration of treatment (time on exposure) and the occurrence of PML. The impact is on the possible risk minimisation measure if this had been confirmed. In addition to the PML risk (potentially fatal Adverse Effect), some other risks emerged during post-marketing period. Risk has increased with several SPC amendments over the 4 years marketing. Long term treatment: some studies (ACD2058g)included a retreatment period (RT) or extended treatment (ET); there were 2 observation periods without treatment: Observation period (OB) and Follow-up (FU); ACD2059g included only 3 periods (FT, ET and FU); the results suggest that patients not responding within 3 months will be less likely to respond to prolonged treatment for another 3 months. In total, data from extended treatment (more than 12 weeks) have been obtained from 4,311 patients in open label uncontrolled studies. Over 600 patients have been treated for more than 1 year including 166 patients treated for more than 2 years and up to 3 years. **2b. The factors to be considered in solving the problem:** **Study design:** no direct comparison with any systemic treatment (standard treatments or new biological). Topical symptomatic treatment was allowed as per investigator in all RCTs. **Adequacy of data sources:** Efficacy data was obtained from 5 double blind, placebo controlled Phase III clinical trials designed to evaluate efficacy of efalizumab as a systemic monotherapy.	CHMP opinion EMEA/CHMP/3552/2009; Rapporteurs' Final Assessment Report EMEA/H/C/00542 PSURs and SPC Variations Efalizumab RMP update Nov 2008 pages 30-40

	Safety data is obtained via the number of adverse event (AE) reports received in post-marketing setting by spontaneous sources (health care professionals, literature, regulatory authorities, etc.) Safety data is based on reported events and so can potentially under represent the number of events. This may be due to poor reporting and sensitivity, and there may be an insufficient timeframe to allow for development of adverse events post long term exposure to efalizumab. However, underreporting of PML is likely to be minimal due to widely circulated documentation to physicians warning the risk of PML. **Disease epidemiology**: Efalizumab is indicated in the treatment of "high need" adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA. It needs to be considered how important/essential it is that efalizumab is available to "high need" patients where other medications may not have worked. **Presence of alternative treatments:** In September 2004, 2 biologic medicines (i.e., etanercept and efalizumab) were approved in the EU for the treatment of plaque psoriasis. Subsequently, infliximab was approved for this indication in September 2005, followed by adalimumab in December 2007. All 4 biologic therapies licensed in the EU are indicated for adult psoriasis. PML cases have been reported with some of these biologicals, but not in their psoriasis indication.	
OBJECTIVES 3. Establish objectives that indicate the overall purposes to be achieved. 4. Identify: a) favourable effects b) unfavourable effects	**3. The aim**: The aim is to evaluate the benefit-risk balance of efalizumab with the use of safety and efficacy data obtained from clinical trials and cumulative post-marketing safety information, from a regulator's perspective and using a quantitative method (MCDA) in a first step (other methods to be tested in a later stage of the efalizumab Task Force). BRAT framework will also be developed in the first step of this Case study. **4a. Favourable effects (i.e. efficacy):** The primary efficacy endpoint is the proportion of subjects with a 75% or more improvement from baseline in the PASI score (PASI75). This endpoint is strongly recommended in conjunction with a validated standardised global score (e.g. PGA) in the EMA GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS INDICATED FOR THE TREATMENT OF PSORIASIS**.** Five pivotal clinical studies evaluating efficacy of efalizumab in moderate to severe psoriasis primarily as systemic monotherapy were submitted (ACD2058g, ACD2059g, ACD2390g, ACD2600g and IMP24011). These studies were double blind, placebo-controlled Phase III trials. In total 2714 patients received efalizumab subcutaneously (SC). These	CHMP Assessment Report EMEA/H/542/A20/28 (Table 1); Market Authorisation/EPAR

	trials with efalizumab all had similar study design. In addition study 24011 had a prospectively defined "high need" population (patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA.) The inclusion and exclusion criteria were comparable. The main inclusion criteria were a minimum Psoriasis Area and Severity Index (PASI) score of 12.0 at screening, a plaque psoriasis covering ≥10% of total body surface area (BSA) and a need for systemic treatment. Other outcomes to be considered include PGA (percentage of patients achieving Physician's Global Assessment clear/almost clear at week 12), OLS (percentage of subjects with Overall Lesion Severity (OLS) rating of Minimal or Clear at week 12). In some studies (ACD 2058g, ACD 2059g, and ACD 2390g) additional endpoints included mean improvement in DLQI (dermatology life quality index) and mean improvement in the frequency and severity subscales of Psoriasis Symptom Assessment (PSA). In study 24011, an additional endpoint was PASI 50 (proportion of subjects with a 50% improvement from baseline in the PASI score (partial responders). **4b. Unfavourable effects (i.e. safety):** averse events reported to be associated or caused by efalizumab (spontaneously reported Adverse Effects are deemed to be causally related to the drug per reporter). Safety issues added to the SPC or strengthened warnings since the initial MAA of efalizumab in the EU are as follows: aseptic meningitis, (opportunistic) infections including tuberculosis, immune mediated haemolytic anaemia, antibody development with vaccinations, interstitial pneumonitis, arthritis, erythema multiforme, inflammatory polyradiculoneuropathy including Guillain Barré like syndrome and Miller Fisher syndrome, facial palsy and Bells palsy during long-term use, severe infections and malignancies, PML. Other unfavourable effects may include overall incidence of AEs per SOC in Clinical Trials at week 12. At the time of the CHMP assessement report, the efalizumab worldwide exposed population was estimated 47,000 patient-years. An evaluation of the exposed population per duration of exposure is available.	CHMP Assessment Report EMEA/H/542/A20/28 (See Table 2 and additional notes for summary); PSURs and SPC variations (See Table 3 and additional notes for summary)
ALTERNATIVES	**5a. Pre-approval**: N/A	N/A

5. Identify the options to be evaluated against the criteria.	**5b. Post-approval**: • do nothing, if the B-R assessment is still positive • limit duration, to 2 years (proposed by MAH based on the observed delay of onset of the 4 reported cases of PML) • Limit duration AND restrict indication to a subset of patients where B-R would still be positive • Suspend/revoke Market Authorisation.	CHMP Opinion EMA/CHMP/3552/2009
CONSEQUENCES 6. Describe how the alternatives perform for each of the criteria, i.e., the magnitude and desirability of favourable effects, the severity of unfavourable effects, and the incidence of all effects.	**Alternative: Do nothing**: implies that B-R balance still considered positive by Rapporteur and CHMP using MCDA quantitative model based on above data. **Alternative: Restrictions:** • (i) 2 year treatment duration limitation: guidance for transition to alternative treatment? • (ii) Target population change; however the indication in EU is already restricted to the defined "high need" population. • (iii) Suspension/revocation of MA: dose tapering ?; risk of rebound effect (rare erythrodermic forms reported upon treatment withdrawal); transition to alternative treatment (not documented, no available data nor guidance). Drug Recall Worldwide in case of revocation of MA in EU and US.	(i) Serono internal document: Risk of PML: analysis of incidence and risk reduction; (ii) no efficacy and safety data, no subgroup analysis.
TRADE-OFFS 7. Assess the balance between favourable and unfavourable effects.	**Judgement that was made about the benefit-risk balance**: Negative Benefit-Risk Balance, voted by CHMP (20 out of 31). B-R assessment to be reiterated using the same data but with a MCDA quantitative method.	CHMP Opinion EMA/CHMP/3552/2009
UNCERTAINTY 8. Report the uncertainty associated with the	**Efficacy**: Uncertainty on the extent of off-label use in patients with less severe conditions, decreasing the benefit part of the balance. No direct comparison with any other systemic treatment, neither standard (cyclosporine, methotrexate, OUVA) nor biologicals. Assessors of B-R in Jan 2009 had indirect comparison with	Efficacy: no source data on off label use. Limited post-marketing studies.

favourable and unfavourable effects.	results of RCT for new biologicals. **Safety**: Uncertainty on the shape of the risk function of PML over time (probably not linear), based on only 4 cases. No true incidence but only reporting rate, although under-reporting is unlikely or very limited due to large communication of this risk to patients and prescribers An internal document provides the patient exposure per duration of treatment based on Sales data.	Safety: Serono internal document: Risk of PML: analysis of incidence and risk reduction
9. Consider how the balance between favourable and unfavourable effects is affected by considering the uncertainty associated with the effects.	**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**: Whichever the uncertainty on efficacy and safety data, all scenarii would decrease the benefit risk balance (underestimated risk, overestimated benefit). If all deterministic measures (derived from measures of central tendency on all the criteria) were set to the favouralbe limits of their confidence intervals, then, clerly, the B-R ratio would improve. However, considering the full range of uncertainty usually leads to a less favourable B-R balance. Threshholds are not considered in multi-criteria decision analysis because these models just compare the benefit-risk balances of the alternatives. Decisions based on single criteria can only be justified if the entire weight of 100% is assigned to that one criterion.	No source data on the under-reporting rate of various AEs (possibly minimal on the major PML risk)
RISK TOLERANCE 10. Judge the relative importance of the decision maker's risk attitude for this medicinal product.	**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, great medical need, risk management plan)**: • Initial MA in 2004 was already controversial (no consensus between Rapporteur and co-Rapporteur) • In January 2009, medical need is covered by several other therapeutic options, and efalizumab has modest efficacy when compared to alternative treatments (indirect comparison with similar endpoints from RCT with new biological) • Psoriasis is not a life-threatening disease though it may have a serious impact on social and professional life • Risk Management Plan with no obvious risk minimisation measures which could be easily and quickly implemented (sub population ?, limitation of treatment to 2 years).	CHMP Opinion and grounds for decision. EMA/CHMP/3552/2009

11. Report how this affected the balance reported in step 9.	**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?):** Safety Advisory Group (SAG, consisting of dermatologists and neurologists) was consulted shortly prior to the final decision. Some have voiced the patient's perspective.	Responses of the Scientific Advisory Group CNS to the CHMP list of questions on Rapitva 7 Jan 2009. EMA/24463/2009
LINKED DECISIONS 12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.	**How this decision might set a precedent or make similar decisions in the future easier or more difficult**: Efalizumab is the first monoclonal antibody ever to be definitively revoked from the market for safety reasons (Tysabri came back with a RMP). The FDA made in US a similar decision to EMA, leading to a US withdrawal from market approximately at the same time as EU and rest of the world. Benefit-Risk balance of immunosuppressive monoclonal antibodies with unknown long term effects in non life-threatening diseases with existing alternative treatments may be questionable over time. Development programmes to be adapted to this situation (design, duration, sub population analysis, etc.)	

Additional notes for Objectives step 4: Identify: a) favourable effects

Table 1. Phase III studies with Elafizumab, Raptiva®

Study	ACD2390g		ACD2058g			ACD2059g			ACD2600g		IMP24011	
Design	12-week, DB, PC RT		12-week, DB, PC RT			12-week, DB, PC RT			12-week, DB, PC RT		12-week, DB, PC RT	
Main inclusion criteria	-Moderate to severe psoriasis -Diagnosis of plaque psoriasis for 6 months -PASI score of ≥ 12 -Baseline ≥ 10% BSA involvement -candidate for systemic treatment								-Moderate to severe psoriasis -PASI score of ≥ 12 -Baseline ≥ 10% BSA involvement -candidate for systemic treatment		-Moderate to severe psoriasis - patients who met the definition for unsuitability of existing systemic therapies based on patient's history of therapy	
Patients	-More male (between 64,8 % and 72,3 %) than female included -More whites (between 84,9 % to 91,6 %) than coloured people were included (from EPAR where only overall figures were presented). -75.9% of subjects had received prior systemic therapy		-54.8% of subjects had received prior systemic therapy			-66.7% of subjects had received prior systemic therapy			-proportion of females was higher in the placebo group than in the verum group -28.4% used MTX -13.4% used systemic retinoids -12.8% used other unspecified systemic therapies -10.3% used systemic corticosteroids -8.7% used ciclosporin -47.5% used UVB -23.0% used systemic PUVA -4.5% used topical PUVA		-Baseline PASI score mean 24.4 -Baseline BSA score mean 38.2 -24% had psoriatic arthritis -98.7% had previously used systemic therapy -35.7% used ciclosporin -93.0% had previous treatment with ≥ 2 therapies -41.1% had previous treatment with ≥ 3 therapies -70.2% used MTX -55.9% used PUVA -48.9% used retinoids	
Co-medication	Allowed concomitant psoriasis treatments were emollient cream, tar or salicylic acid preparations for the scalp, and low-potency topical corticosteroids for lesions on the face, hands, feet, axillae, or groin.								None/unknown			
Primary efficacy	The PASI 75 response rate (i.e., the proportion of subjects with a 75% reduction in PASI) at week 12											
Treatment Results (N)	Pl	E 1.0 mg	Pl	E 1.0 mg	E 2.0 mg	Pl	E 1.0 mg	E 2.0 mg	Pl	E 1.0 mg	Pl	E 1.0 mg
	187	369	170	162	166	122	232	243	236	450	264	529
≥ PASI 75 (%)	**4.3**	**26.6** [a]	**2.4**	**38.9** [a]	**26.5** [a]	**4.9**	**22.4** [a]	**28.4** [a]	**3.0**	**23.5** [a]	**4.2**	**31.4** [a]
PGA clear /almost clear** (%)	5.3	33.1 [a]	4.1	38.9 [a]	30.1 [a]	4.1	22.4 [a]	28.4 [a]			2.7 [b] 7.5 [c]	25.7 [b] 29.9 [c]

Source: Raptiva®, EPAR

Pl = placebo, E 1.0 mg = efalizumab 1.0 mg/kg/wk SC, E 1.0 mg = 2.0 mg/kg/wk SC
* PUVA = phototherapy combining psoralens and ultraviolet light A, ** 0 or 1 on 0-5 scale
[a] p< 0.001 for 1.0 mg or 2.0 mg in comparison with placebo [b] Subjects resistant or intolerant or contraindicated for systemic therapy (n = 526) and [c] other subjects (n=267)

Additional notes for Objectives step 4: Identify: a) unfavourable effects

Table 2. Reporting of adverse events	
Source	**Unfavourable Effect**
PSUR 1	meningitis aseptic, headaches
PSUR 2	opportunistic infections and tuberculosis; immune mediated haemolytic anaemia, , arthritis, interstitial pneumonitis, and erythema multiforme; model of T-cell dependent antibody response was lowered during efalizumab treatment, updates to antibody response during immunisation (Tetanus toxoid booster vaccination and Pneumococcal vaccination and reduction in cellular immune response)
PSUR 4	increases the risk or severity of infections, e.g. tuberculosis, pneumonia, and reactivate latent chronic infections; cases of arthritis have been observed during treatment or after discontinuation of efalizumab; it is unclear whether efalizumab is associated with an increased risk of lymphoproliferative disorders in psoriasis patients.
PSUR 9 and PSUR 10	next to the identified PML cases, three cases of tuberculosis have been reported, which is a high rate in perspective of the limited cumulative exposure of efalizumab of about 47,000 patient-years (Data Lock Point on 30.9.2008). Also lymphoma, meningitis and CNS infections in general remain a concern. Furthermore increased frequencies of infections, non-melanoma skin cancer and malignancies are mentioned in relation with efalizumab.
MAH global safety database	4 cases of inflammatory neuropathy syndromes, including two cases of myelitis identified. Additionally, two cases of Guillain Barre Syndrome and a case of Miller Fisher syndrome
MAH cumulative review of facial palsy	facial palsy (Bell's palsy) with "uncommon" frequency

The most frequently reported spontaneous AEs during the postmarketing period:

- 'Skin and Subcutaneous Tissue Disorders' (24.3%)
- 'General Disorders and Administration Site Conditions' (18.3%)
- 'Nervous System Disorders' (12.4%)
- 'Musculoskeletal and Connective Tissue Disorders' (11.4%)
- 'Infections and Infestations' (9.6%) and 'Gastrointestinal Disorders' (7.0%).

The high frequency of skin AEs is attributable to skin disorders, such as psoriasis flare-up, erythemathous rash, rebounds or other psoriasis-related adverse events. Less than 10% of all skin disorders were reported as serious events. Similar differences between the total number of events and those assessed as serious were observed for other organ classes, such as 'general and administration site disorders (e.g. weakness, fatigue, and flu-like symptoms), 'musculoskeletal disorders' (myalgia, arthralgia) and 'nervous system disorders' (headache), with 10%, 22% and 13% of reported cases, respectively, considered serious.

Cases of Progressive multifocal leukoencephalopathy (PML) and related disorders

No cases of PML have been reported with the use of efalizumab in developmental clinical trials. There is no reported case of PML in a general psoriasis population. However, since September 2008, four cases of progressive multifocal leukoencephalopathy (PML) have been reported by the MAH; of these reported cases, three were serologically confirmed. Three of them lead to the patient's death. In the October 2008 meeting of the CHMP, the SPC was strengthened for PML and a Dear Health Care Professional (DHPC) letter was circulated informing about the occurrence of PML with efalizumab.

PML was seen in patients using efalizumab for about three to four years. Taking into account the total number of patients using efalizumab for about four years is approximately 1000 patients, the incidence could be one PML case per 500 patients in the population of efalizumab using the drug for approximately four years. As a consequence the MAH proposes to discontinue efalizumab after two-year treatment. The proposal includes rotational treatment with systemic medications including light therapies and topical medications to reduce the cumulative toxicity of anti-psoriatic treatment

The cases show how difficult it is to diagnose PML. It is also not clear that if diagnosed the sequel of the disease can be reversed (e.g. by plasma exchange). The clinical signs and symptoms of PML are usually non-specific and may present with a variable clinical depiction. The fact that PML under efalizumab was observed only after four years of treatment, may be a chance finding. Approximately 85% of the healthy population carries the JC-virus. In the reported cases, the infection may have been reactivated or newly acquired.

Section 4.4 modifications presented in PSUR 10

> "Use of Raptiva® may be associated with an increased risk of Progressive Multifocal Leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML (such as impaired cognition, visual disturbances, hemiparesis, altered mental state or behavioural changes). If a patient develops PML, the dosing of Raptiva® must be permanently discontinued."

Section 4.8 modifications presented in PSUR 10

"JC virus infection resulting in progressive multifocal leukoencephalopathy" was added to the section "Adverse reactions identified during post-marketing surveillance."

Table 3. Reported cases of PML

Reported reaction	Onset latency	Event Outcome	Concomitant medication / relevant past drugs	Co-morbidities / Risk factors
Progressive multifocal leukoencephalopathy'	4 years	Fatal	Pravastatin, aspirin	Coronary artery disease, hyperlipidemia, angioplasty, stent placement
Progressive multifocal leukoencephalopathy Degenerative neurological symptoms	>3.75 years	Fatal	Statins, temazepam, lexapro, aspirin, estrogens	Hyperlipidemia, diverticulum, depression
'Progressive multifocal leukoencephalopathy' was suspected	4 years	Fatal	Zoloft, nexium, statins, aspirin	Hyperlipidemia, hypertension, sleep apnoea syndrome, chronic obstructive pulmonary disease, basal cell carcinoma
Progressive multifocal leukoencephalopahty	3.25 years	Hospitalised	Acitretin (2000-2001); fumaric acid in 2002 and methotrexate (2002-2003)	Obesity

Cases of Encephalopathy

A total of three other reports of encephalopathy were identified in the safety database. In none of the three cases of 'encephalopathy' the reporting physicians suspected PML; moreover, Magnetic Resonance Imaging (MRI) findings in first two patients and a negative brain biopsy of the first patient were not consistent with PML.

Table 4. Events of "Encephalopathy" other than PML reported with efalizumab

Case	Reported reaction	Onset latency	Event Outcome	Concomitant medication / relevant past drugs	Co-morbidities / Risk factors
No 1	Encephalopathy	>1 year	Fatal	Topicals	Charcot Marie Tooth, neuropathy (diagnosed at age 16), hypothyroidism, anxiety, polyarthritis
No 2	Encephalopathy syndrome	Not reported	Recovering	Diclofenac, enalapril maleate, hydrochlorothiazide, aspirin	Gout, arthralgia
No 3	Staphylococcal sepsis (cause of death) 'Encephalopathy' listed among other associated events	16 months	Fatal	Statins, atenolol, famotidine, paroxetine	Status post CA bypass, arteriosclerotic peripheral vascular disease, hypertension, hypercholesterolemia, hypothyroidism, tobacco use, seasonal allergic rhinitis, avascular necrosis, status post bilateral total hip arthroplasty, septic prosthetic arthritis with associated iliopsoas abscess

Cases of Encephalitis

The search identified five reports of encephalitis in the safety database during the post-marketing surveillance.

Table 5. Events of "Encephalitis" reported with efalizumab

Case	Reported reaction	Onset latency (weeks)	Event Outcome	Concomitant medication / relevant past drugs	Co-morbidities / Risk factors
No 1	Encephalitis, meningitis	6 weeks	Fatal	Enalapril	Chronic teeth infection, hypertension
No 2	Encephalitis	5 months	Recovering	None reported	Alcoholism, primary biliary cirrhosis
No 3	Encephalitis	4 years	Recovering	Albuterol, restoril, topicals, trazadone	Pneumonia, asthma, depression
No 4	Encephalitis herpes	28 months	Not Reported	None reported	Herpes simplex
No 5	Encephalitis	3 months	Recovered with sequelae	Cellcept, prednizone, prograf, valtrex / Tacrolimus	Chronic renal failure, renal transplant, diabetes

Although none of the cases were suggestive of PML, three cases concerned serious infections. The role of efalizumab could therefore not be excluded.

Cases of Infections and Infestations

The total number of patients experiencing serious infections reported during the post-marketing period corresponds to a reporting rate of serious infections of about 0.61 per 100 patient-years. About 18% of all infections and 24% of serious medically confirmed infections reported with the use of efalizumab relate to different types of pneumonia or lung infection. The evolution of infections observed during efalizumab treatment may be severe, and in isolated cases, the outcome has been fatal. Due to the selective immunosuppressive mechanism of action of efalizumab, it is possible that efalizumab has played a role in the evolution of these cases.

Cases of opportunistic infections have also been reported during treatment with efalizumab. About 80% of all opportunistic infections cluster around three main groups: fungal infections, tuberculosis and herpes virus infections (including herpes zoster and varicella).

Cases of Cerebrovascular disorders

Cerebrovascular events occurred in patients with significant risk factors, such as hypertension, diabetes, chronic cardiac failure, atrial fibrillation, hypercholesterolemia, hyperlipidemia, as well as history of previous myocardial infarction or pulmonary embolism, concomitant use of methotrexate or tamoxifen, as well as smoking and obesity. Patients with psoriasis tend to present higher prevalence of cardiovascular risk factors. In general, it has been shown that the risk of cerebrovascular accidents is increased in psoriasis patients.

Cases of Neurological disorders

In the SPC for efalizumab facial palsy and inflammatory polyradiculoneuropathies (including Guillain Barré syndrome) have been described as events observed post-marketing.

2 PhRMA BRAT Framework

Sources

(Coplan et al., 2011, Levitan et al., 2011) BRAT Framework for Benefit-Risk Assessment: User's Guide, PhRMA BRAT software, PhRMA BRAT Software User's Guide.

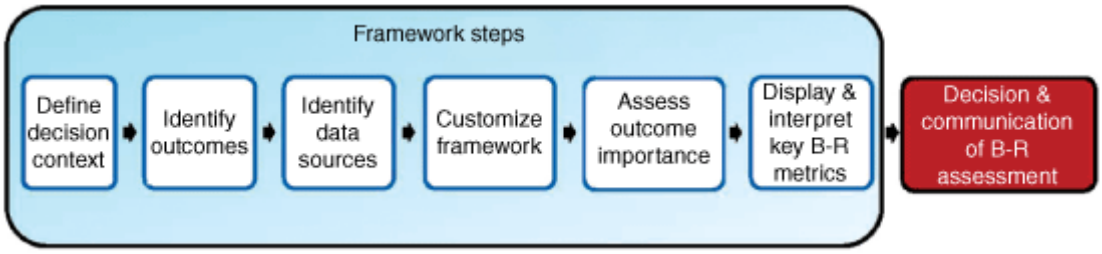
Introduction

Between 2005 and 2010, the Pharmaceutical Research and Manufacturers of America (PhRMA) Benefit Risk Action Team (BRAT) developed a benefit/risk Framework. This framework is essentially a set of processes and tools for regulatory or clinical decision-makers to use to select, organise, summarise, interpret and understand evidence that is relevant to decisions based on benefit–risk assessments. It is adaptable and can incorporate the perspectives of important stakeholders, such as patients and health-care professionals by combining qualitative and quantitative information including study outcomes and preference weights. It is postulated that the framework is particularly useful for complex scenarios with emerging safety information , due to its capacity to a) communicate effectively both benefits and the risks and b) perform an informed balanced benefit/risk assessment outside of the actual framework.

Method

The PhRMA BRAT framework comprises of a series of 6 steps. The key steps in the process are outlined in Figure 1. This work will present the steps of the PhRMA BRAT framework, and describe how the framework was applied to the case study of efalizumab to perform a benefit-risk assessment.

Figure 1 Processes in the PhRMA BRAT framework



(Coplan et al., 2011)

Application to case study

Preparing to use the BRAT framwork

A preliminary preparation before embarking on the PhRMA BRAT framework is to determine the scope of the project. That is, how the framework will be used and pre-specifying the project outputs, such as internal governance, regulatory interaction, or clinical planning needed to determine the breadth and depth of data required. This preparation was not included in our use of the PhRMA BRAT framework because it had been previously addressed in earlier stages of taskforce planning.

2.1 Step 1: Define the decision context

The first step of the PhRMA BRAT framework is to define the decision context, the output of which is presented in Table 6. This involves defining the objective and assumptions of assessment by specifying and defining the therapeutic context, comparator, time horizon (i.e. the duration of exposure to the product and the time period over which benefit–risk events are measured), and additionally noting whose perspective is to be taken (e.g. patient, regulator, payor or sponsor). The perspective is of utmost importance, as this will shape the decision process by determining which comparators, attributes, outcomes and measurement endpoints, and preference weights will be applied. One limitation is that when the framework was applied to our case study, Step 1 did not have a field where a specific time point could be specified (i.e. 2009) which would allow for a clearer description of the context when retrofitting decision-making within an historical scenario.

Table 6 Step one: Define decision context	
Objective	To evaluate the benefit-risk balance of efalizumab with the use of safety and efficacy data obtained from clinical trials and cumulative post-marketing safety information on 2009, in order to examine the impact of utilizing a structured benefit-risk assessment.
Drug	Efalizumab (Raptiva®)
Dose	An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight, subcutaneously
Drug class	Monoclonal antibody
Formulation	All (e.g. GNE SC, XOMA SC)
Indication under consideration	Moderate to severe plaque psoriasis
Intended patient population of interest (including contraindications to treatment and baseline disease characteristics)	“high need” adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate and PUVA
Comparator(s)	Placebo
Time horizon (for outcomes to occur), i.e. time frame for treatment and for follow-up for relevant clinical outcomes	12 weeks for PASI 75 (efficacy), 3 years for PML (safety)
Decision-maker perspective (e.g. regulator, sponsor, patient, physician)	Regulator

2.2 Step 2: Identify and select benefit and risk outcomes and associated measures

The second step of the PhRMA BRAT framework is to identify and select benefit and risk outcomes and associated measures. In this step a list of potential outcomes for assessment is compiled via literature reviews, regulatory precedents and meetings with clinical experts. The pool of possible outcomes includes all outcomes, whether "known" or "potential", and may include possible outcomes not relevant to the benefit-risk assessment. As mentioned, they can be compiled from internal company and external documentation, literature reviews, consultations with experts and patients, as well as from knowledge of similar drugs in the same class, or other drugs used in similar indications. This list is later reduced by evaluating which outcomes to be included or excluded from the value tree in later steps. The included outcomes are those thought to most importantly influence the benefit-risk balance. All of the inclusion and exclusion criteria must be documented.

For the first step, it was necessary for the efalizumab case study to deviate from the instructions. The historical regulatory scenario and decision context specified in Step 1 placed limitations on how the PhRMA BRAT framework could be adopted:

Firstly, the perspective of the regulator would have been informed by the favourable and unfavourable effects data provided via clinical trials and post-marketing surveillance. This information was documented in regulatory documents such as EPARs, Scientific Discussion, and changes to the Summary of Product Characteristics (SPC). Therefore the taskforce did not obtain a pool of outcomes from literature reviews, regulatory precedents and meetings with clinical experts as instructed by the PhRMA BRAT method. Instead, regulatory documents were closely examined to specifically address the how the regulator would have considered the benefit risk balance with the data which would have been available to them at the time.

Secondly, the PhRMA BRAT framework suggests listing known or potential outcomes relevant to public health, physicians, and patients. This can result in the inclusion of outcomes deemed important by specific stakeholder groups. However, our taskforce refrained from this as we wanted the perspective to be specific to only the regulator and the data they could have accessed at the time of decision-making. This is a traditional perspective, although it is worth noting that explicitly discussing the outcomes for inclusion between stakeholders can result in a beneficial harmonisation between groups.

Thirdly, the data broadly addressed the outcome of "favourable effects" in terms of efficacy with "unfavourable effects" in terms of safety. The taskforce had previously complied data contained within the regulatory documents into an effects table. However, it became evident that information compiled within effects table placed a primary emphasis on measures rather than outcomes. That is, the data presented to the regulator was often in terms of measures e.g. PASI75, PGA etc., which was then broadly covered with either an umbrella outcome term of "efficacy", or one of "safety". Therefore, we did not perform the suggested task of selecting measures to characterise outcomes, as we had already collected measures of relevance to our scenario.

Measures

Table 7 contains a list of measures deemed most likely to influence the benefit-risk balance given the decision context. This list contains all the measures present on the effects table which were considered at the time of decision-making by the regulator; e.g. drug specific safety issues, changes to SPC, reported spontaneous AEs.

Table 7 Measures most likely to importantly influence the benefit-risk balance

Favourable effects:

- PASI75
- PGA
- OLS
- DLQI
- PASI50

Unfavourable effects:

- ADR1 (mild to moderate)
- ADR2 (serious)
- Meningitis aseptic
- Serious infections including pneumonia, sepsis, cellulitis
- Opportunistic infections including fungal infections, tuberculosis, herpes virus infections, EBV, CMV
- Serious thrombocytopenia
- Immune haemolytic anaemia
- Psoriasis severe forms (erythrodermic, pustular)
- Nervous System disorders including Inflammatory polyradiculopathy, Facial Palsy, GBS, Fisher Miller Syndrome
- Interstitial lung diseases including lung infiltration, pulmonary fibrosis
- Serious cases of psoriasis exacerbation or rebound
- Brain infections including Encephalitis and PML

The framework distinguishes between measures which count outcome events and count patients. It is important to note that for each measure within this case study the units varied for the clinical trial and surveillance data presented within regulatory documents. Therefore, there was an extremely mixed approach to units in the case study, ranging from percent per 100 patient years, to number of cases, to percent. The measures also vary with different time periods and populations.

Composite measures are frequently reported in regulatory documents. Although the framework acknowledges composite measures to be useful when one outcome may not adequately capture the most relevant attribute for a product, it warns that it might introduce difficulty when making important trade-offs in Step 5 of the PhRMA BRAT framework, especially if the outcomes it contains have different effects on patients. Measures are frequently placed together into composite groups within the effects table.

Value tree

It is possible to draw up an initial value tree (Figure 2) which contains the benefit and risk measures from Table 7. This tree will be further developed in the subsequent steps to only include available, precisely defined, reliable and accurate end-point measures available to the regulator at time of decision-making.

The tree should exclude outcomes which are considered components of another included outcome, and outcomes which are similar to prevent double counting and overestimation of effects. Our methods deliberately diverged from the method at this point to include all potential outcomes and disregard double counting and overestimation. This is because we wished to present a full range of measures in key benefit–risk summary table the forest plot diagram within Step Six. This allows for a full comparison of measures to examine how the visual representation of similar measures may vary.

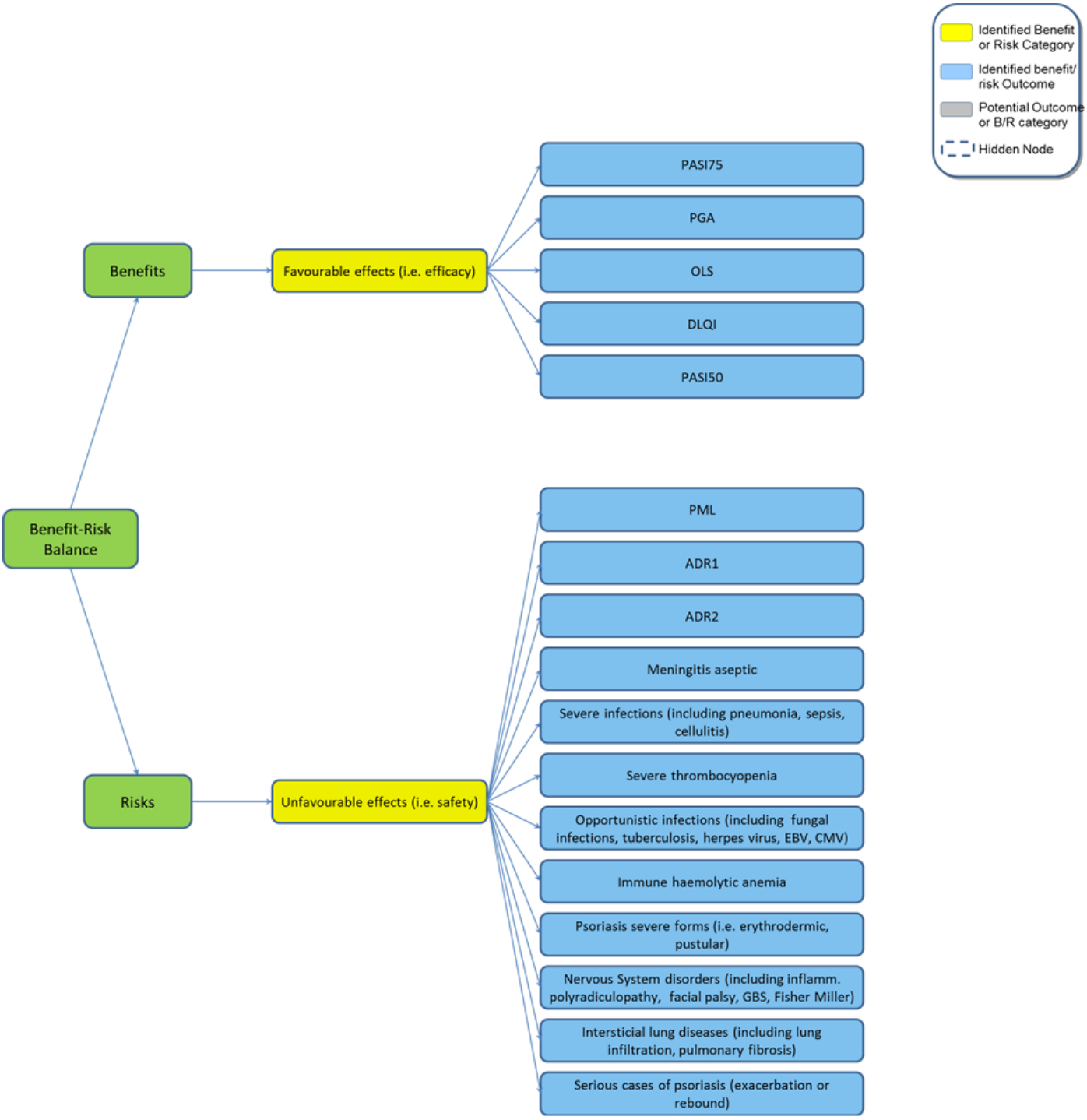


Figure 2. Initial value tree built using BRAT framework tool

2.3 Step 3: Identify and extract data sources

The third step describes the identification and selection of data sources, in addition to organising them and extracting the relevant data. For the case study of efalizumab, any document which would have been available to the decision-maker, i.e. the regulator, was included if was publically available at the time of decision-making, or could be publically provided upon request. Regulatory documents containing favourable and unfavourable information from clinical trials and post-marketing surveillance were identified, and documented. The relevant data was then extracted.

Inclusion of measures

Rationale for inclusion or exclusion of data was documented (Table 8). Specifically, measures were only included if they had sufficient information to completed the required data source table fields in Step 4, e.g. background epidemiology of placebo known.

Table 8 Measures and inclusion

Measure	Source	Inclusion	Rationale
PASI75	Clinical trials	Yes	Complete data
PGA	Clinical trials	Yes	Complete data
OLS	Clinical trials	Yes	Complete data
DLQI	Clinical trials	No	Average and standard deviation missing
PASI 50	Clinical trials	Yes	Complete data
ADR1	ISS	Yes	Complete data
ADR2	ISS	No	Percentage of events in placebo group not given; percentage of events for efalizumab not precise (range given)
Meningitis aseptic	PSUR10	No	Background epidemiology not known
Serious infections including pneumonia, sepsis, cellulitis	ISS	Yes	Complete data
Opportunistic infections including fungal infections, tuberculosis, herpes virus infections, EBV, CMV	PSUR10	No	RMP only states background epidemiology of tuberculosis; background epidemiology of other conditions not known
Serious thrombo cytopenia	PSUR10	No	Background epidemiology not known
Immune haemolytic anemia	PSUR10	No	Background epidemiology not known
Psoriasis severe forms (i.e. erythrodermic, pustular)	ISS	Yes	Complete data
Nervous System disorders including Inflammatory polyradiculopathy, Facial Palsy, GBS, Fisher Miller Syndrome	PSUR10	No	Background epidemiology not known
Interstitial lung diseases including lung infiltration, pulmonary fibrosis	PSUR10	No	Background epidemiology not known
Serious cases of psoriasis exacerbation or rebound	PSUR10	No	Background epidemiology not known
Brain infections including Encephalitis and PML	PSUR10	Yes	Complete data

Data source table

The PhRMA BRAT guidelines state that a data source table should be completed, which includes all study and publication details. However, this case study used the PhRMA BRAT software that does not have the capacity to store information on the data sources, and instead contains a spreadsheet to store details of the measures (Table 9).

Table 9 Data table

Outcome name	Treatment 1 rate point estimate	Treatment 1 rate lower CI	Treatment 1 rate upper CI	Treatment 1 number of patients	Treatment 1 number of events	Duration treatment 1
PASI75	0.28	0.18	0.41	1742	485	12
PGA	0.3	0.18	0.46	1742	531	12
OLS	0.29	0.18	0.44	1742	508	12
PML	$8.51\ 10^{-5}$	$1.72\ 10^{-6}$	$1.69\ 10^{-4}$	47000	4	PMS
ADR1	0.41	0.39	0.43	1742	714	12
Psoriasis severe forms	0.03	0.02	0.04	1742	56	12
Outcome name	**Treatment 2 rate point estimate**	**Treatment 2 rate lower CI**	**Treatment 2 rate upper CI**	**Treatment 2 number of patients**	**Treatment 2 number of events**	**Duration treatment 2**
PASI75	0.04	0.02	0.06	979	36	12
PGA	0.05	0.03	0.09	979	51	12
OLS	0.04	0.02	0.06	979	36	12
PML	$4.40\ 10^{-6}$	$3.10\ 10^{-6}$	$5.70\ 10^{-6}$	10000000	44	PMS
ADR1	0.24	0.21	0.27	979	235	12
Psoriasis severe forms	0.01	0.01	0.02	979	14	12
Outcome name	**Risk difference point estimate**	**Risk difference lower CI**	**Risk difference upper CI**	**Relative risk point estimate**	**Relative risk lower CI**	**Relative risk upper CI**
PASI75	0.24	0.15	0.36	7.82	5	12.38
PGA	0.25	0.14	0.4	5.78	3.6	9.34
OLS	0.25	0.15	0.39	7.81	4.73	13.27
PML	$8.07\ 10^{-5}$	$-2.70\ 10^{-6}$	$1.64\ 10^{-4}$	19.34	6.95	53.83
ADR1	0.17	0.13	0.21	1.71	1.51	1.93
Psoriasis severe forms	0.02	0.01	0.03	2.25	1.26	4.02

Within this table it is very interesting to note that the PML risk difference is not significant, and the lower 95% confidence interval is negative. However, the relative risk for PML is significant.

With the data available for each measure, 95% confidence intervals, point estimates, risk differences, and relative risks were calculated using the formulae listed in Table 10. Additionally, a Bayesian mixed effects metaanalysis was performed for PASI75, PGA and OLS.

Table 10 Definitions and equations used within the data source table

Column	Description	Formula
Outcome	Outcome of interest	
Study	Name/code of study	
Treatment 1 rate point estimate (TR_R)	Probability of having an event in the efalizumab arm of the trial	ev_{arm}/n_{arm}
Treatment 1 rate lower/upper CI	Gives the upper and lower confidence intervals of the treatment rate point estimate for efalizumab arm	$TR_R \pm 1.96\sqrt{\frac{TR_R(1-TR_R)}{n_R}}$
Treatment 1 number of patients (n_R)	Number of patient in the efalizumab arm	
Treatment 1 number of events (ev_R)	Number of events of specified outcome	
Treatment 2 rate point estimate (TR_P)	Probability of having an event in the Placebo arm of the trial	
Treatment 1 rate lower/upper CI	Gives the upper and lower confidence intervals of the treatment rate point estimate for Placebo arm	$TR_P \pm 1.96\sqrt{\frac{TR_P(1-TR_P)}{n_P}}$
Treatment 1 number of patients (n_P)	Number of patient in the Placebo arm	
Treatment 1 number of events (ev)	Number of events of specified outcome	
Risk difference point estimate (RDiff)	Difference in risk of having specified event between efalizumab arm and Placebo arm	$TR_R - TR_P$
Risk difference lower/upper CI	Gives the upper and lower confidence interval of the risk difference point estimate	$RDiff \pm 1.96\sqrt{\frac{ev_R(n_R-ev_R)}{n_R^3}+\frac{ev_P(n_P-ev_P)}{n_P^3}}$
Relative risk point estimate (RR)	Is the relative risk of developing specified outcome in the efalizumab arm when compared to the placebo Arm	$RR = \frac{(ev_R/n_R)}{(ev_P/n_P)}$
Relative risk lower/upper CI	Gives the upper and lower confidence interval of the relative risk point estimate	$e^{\ln RR \pm 1.96\sqrt{\left(\frac{1}{ev_R}-\frac{1}{n_R}\right)+\left(\frac{1}{ev_P}-\frac{1}{n_P}\right)}}$

2.4 Step 4: Customise framework

Step four (Table 11) customises the framework. The initial value tree created in step two is modified to account for clinical expertise and the data reviewed in step three. Outcomes considered irrelevant to the benefit- risk assessment or stakeholder groups are either refined to obtain relevance or removed.

Application to case study

For our case study, we were constrained by the quality of data sources. Measures with incomplete data (e.g. no details on background epidemiology) were removed. Table 11 lists the final outcome measures used.

Table 11 Final list of outcome measures	
PASI75	Proportion of patients who achieve a 75% reduction in PASI scores. The PASI score is derived by evaluating erythema, scaling and thickness and then weighting the coverage according to the area covered, i.e. head, trunk, upper extremities and lower extremities. The scores can range from 0 (least severe) to 72 (most severe).
PASI50	Proportion of patients who achieve a 50% reduction in PASI scores after two weeks. See PASI75 scoring of the PASI.
PGA	Static PGA is a measure of the psoriatic lesions taken at a single timepoint. The scores can range from 7 (least severe) to 1 (most severe).
OLS	The OLS is a global rating of psoriasis severity according to plaque elevation, scaling, and erythema at a given time point. The scores can range from 0 (least severe) to 5 (most severe).
PML	Progressive multifocal leukoencephalopathy. A demyelinating disease caused by reactivation of the John Cunningham virus.
ADR1	Mild to moderate dose related acute flu-like symptoms.
Psoriasis severe forms	E.g. erythrodermic, pustular

As stated in the previous step, there are differences in the design, and outcome measures between clinical trials and post-marketing surveillance. For example, two of the clinical trials pooled the data for efalizumab 1mg/kg/wk, and efalizumab 2mg/kg/wk when calculating unfavourable effects for examples such as ADR1 and psoriasis severe form. It is assumed the effect will be small and result in a minor overestimation of adverse events. Additionally, the follow up time for clinical trials was set to twelve weeks, whereas the follow up time for post-marketing surveillance was cumulative and lasted for 47,000 patient-years.

Tuning was made accordingly with the data available and is displayed below (Figure 3).

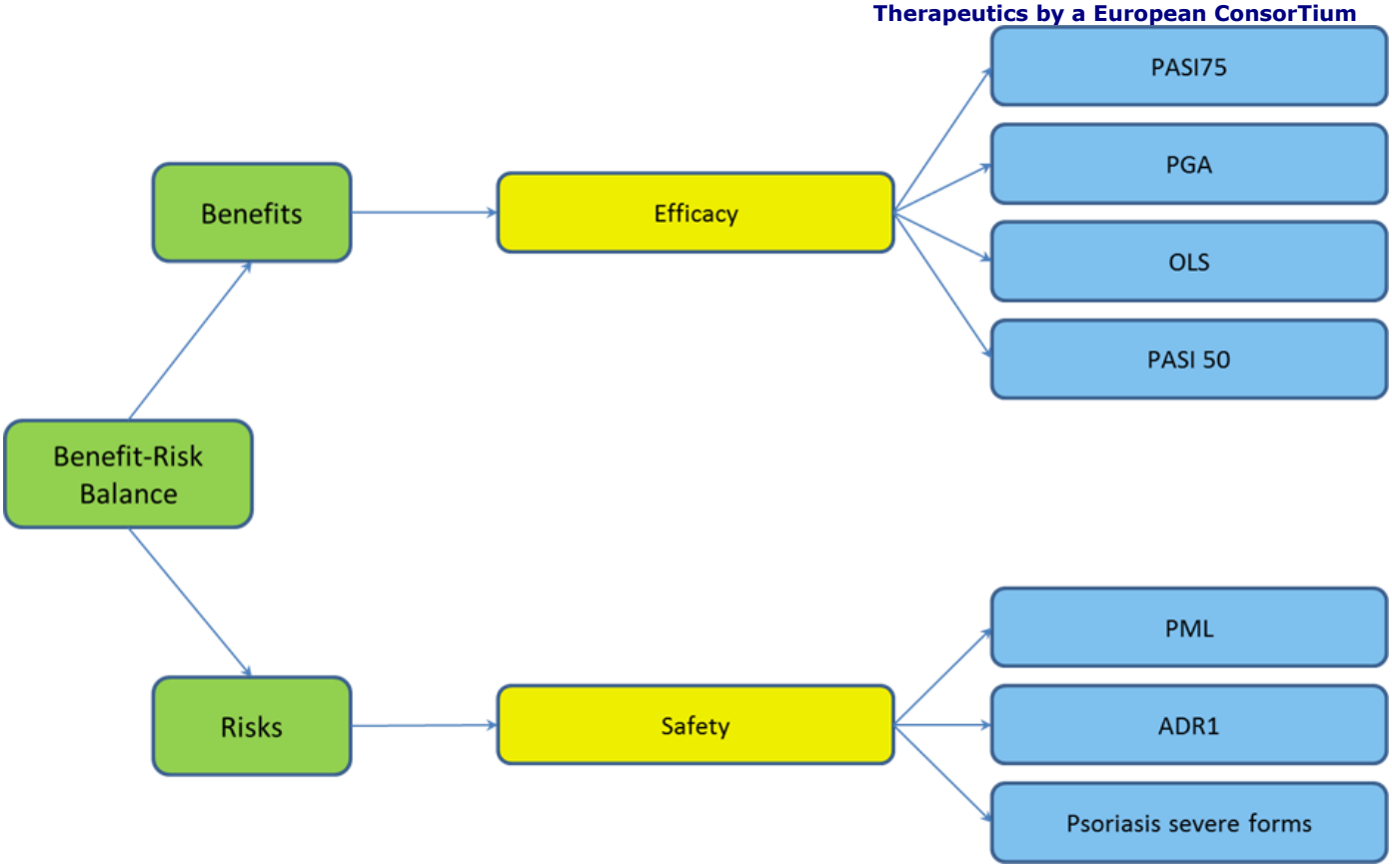


Figure 3 Modified value tree

2.5 Step 5: Assess outcome importance

MCDA

In this step, outcomes are assessed for their importance to decision-makers and other stakeholders, and the subsequent rankings and weightings are applied to the decision tree. Outcomes are differentially weighed relative to one another, according to stakeholder group. Weights from multiple stakeholder groups can provide the basis for a sensitivity analysis over different stakeholder perspectives. It is important to note that the PhRMA BRAT framework does not advocate a specific method to weigh the preferences of outcomes in the value tree.

2.6 Step 6: Display and interpret key benefit-risk metrics

Table 12 places the source data into a key benefit–risk summary table which summarises the key information in source data required to quantify outcomes in the value tree. The table aids interpretation of benefits and risks; Treatment A is efalizumab, Treatment B is placebo. The use of such framework can increase the transparency, predictability and consistency with which benefit-risk assessments are conducted.

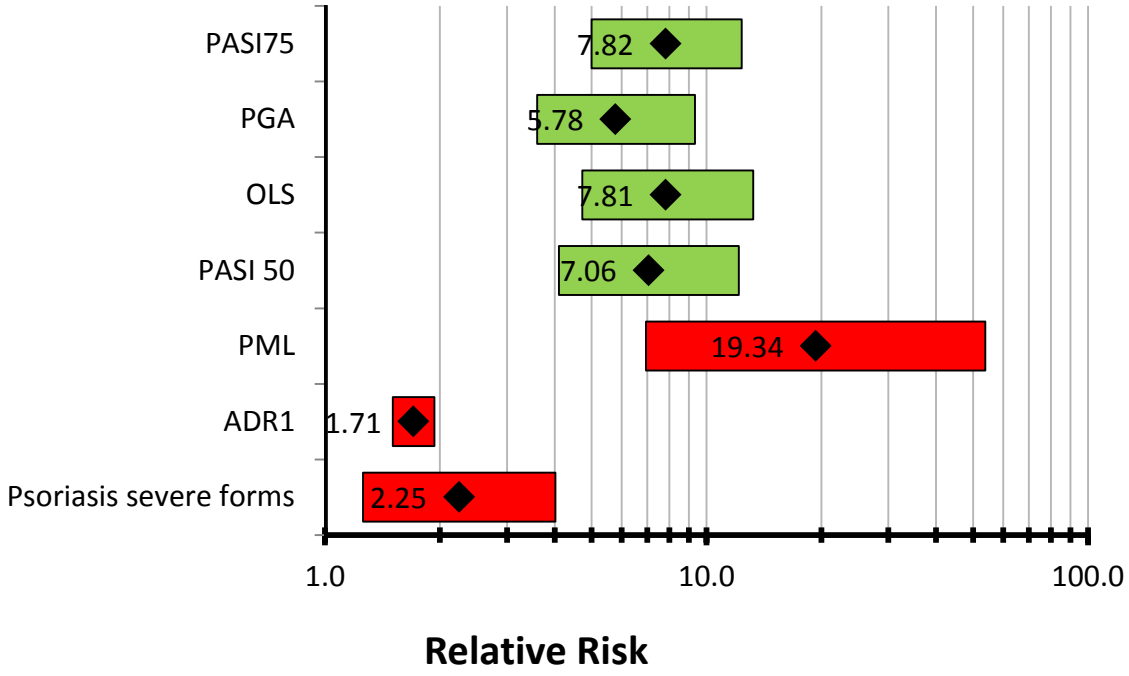
Table 12 Key benefit-risk summary table

		Outcome	Treatment A Risk / 1000 pts	Treatment B Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Benefits	Efficacy	PASI75	280	36	244	(151, 362)	7.819	(4.999, 12.380)
		PGA	305	52	251	(141, 396)	5.778	(3.602, 9.337)
		OLS	292	37	254	(145, 392)	7.813	(4.731, 13.270)
		PASI 50	567	200	367	(319, 415)	7.064	(4.105, 12.154)
Risks	Safety	PML	0	0	0	(0, 0)	19.342	(6.950, 53.830)
		ADR1	410	240	170	(135, 205)	1.708	(1.507, 1.935)
		Psoriasis severe forms	32	14	18	(7, 29)	2.248	(1.258, 4.017)

The framework states that the key benefit-risk summary table and forest plot delivers easily interpretable information to stakeholder groups-- such as patients and healthcare professionals, so they can make informed decisions based on their own preferences. However, interpreting odds ratios and 95% confidence intervals can be challenging.

Forest plot

The forest plot records all of the measures on a standardised scale, allowing for the evaluation of each measure relative to other measures.



3 Effects table: Criteria Definitions and Effects of Placebo and Raptiva 1mg/kg/wk

	Name	Description	Source	Patient population	Fixed Lower†	Fixed Upper†	Units	Placebo (pts number)	Efalizumab 1mg/kg/wk (pts number)
Favourable effects	PASI75*	Percentage of patients achieving 75% reduction in baseline PASI **at week 12** The PASI is a measure of the average redness, thickness, and scaliness of the lesions (each graded on a 0–4 scale), weighted by the area of involvement	ACD2390g	Moderate to severe plaque psoriasis candidate for systemic treatment	0	100	%	4.3 (175)	26.6 (345)
			ACD2058g	"	0	100	%	2.4 (151)	38.9[a] (149)
			ACD2059g	"	0	100	%	4.9 (111)	22.4[a] (211)
			ACD2600g	"	0	100	%	3.0 (236)	23.5[a] (450)
			IMP24011	Moderate to severe plaque psoriasis candidate for systemic treatment + "high need" subgroup	0	100	%	4.2 (264) 2.7(184)	31.4[a] (529) 29.5(342)
	PGA	Percentage of patients achieving Physician's Global Assessment clear/almost clear at week 12 This is a seven point scale with 7 being	ACD2390g	Moderate to severe plaque psoriasis candidate for systemic treatment	0	100	%	5.3	33.1[a]
			ACD2058g	"	0	100	%	4.1	38.9[a]

Name	Description	Source	Patient population	Fixed Lower†	Fixed Upper†	Units	Placebo (pts number)	Efalizumab 1mg/kg/wk (pts number)
clear and 6 almost clear, 5 mild, 4 mild to moderate, 3 moderate, 2 moderately severe and 1 being severe psoriasis.		ACD2059g	"	0	100	%	4.1	22.4 [a]
		IMP24011	Moderate to severe plaque psoriasis candidate for systemic treatment + "high need" subgroup	0	100	%	7.5 [c] 2.7 [b]	29.9 [c] 25.7 [b]
OLS Subjects with Overall Lesion Severity (OLS) rating of Minimal or Clear at FT Day 84)		ACD2058g XOMA SC	Moderate to severe plaque psoriasis candidate for systemic treatment	0	100	%	2.9	32.1 [a]
		ACD2059g XOMA SC	"	0	100	%	4.4	24.2
		ACD2390g GNE SC	"	0	100	%	3.2	25.7
		IMP24011	Moderate to severe plaque psoriasis candidate for systemic treatment + "high need" subgroup	0	100	%	5 2.7	34.8 21.3
DLQI (Dermatology Life Quality Index)		ACD 2058g	Moderate to severe plaque psoriasis candidate for systemic treatment	0	100	%	2.1	5.3

Name	Description	Source	Patient population	Fixed Lower†	Fixed Upper†	Units	Placebo (pts number)	Efalizumab 1mg/kg/wk (pts number)
		ACD 2059g	Moderate to severe plaque psoriasis candidate for systemic treatment	0	100	%	1.7	5.5
		ACD 2390g	Moderate to severe plaque psoriasis candidate for systemic treatment	0	100	%	1.6	5.6
		IMP 24011	Moderate to severe plaque psoriasis candidate for systemic treatment + “high need” subgroup	0	100	%	2.5 2.3	6.2 5.4
PASI 50 Percentage of patients achieving 50% reduction in baseline PASI **at week 12**		IMP24011	Moderate to severe plaque psoriasis candidate for systemic treatment + “high need” subgroup	0	100	%	20 12	56.7 52

	Name	Description	Source	Patient population	Fixed Lower†	Fixed Upper†	Units	Placebo (pts number)	Efalizumab 1mg/kg/wk (pts number)
Unfavourable effects	ADRs	Mild to moderate dose related acute flu-like symptoms	ISS (all RCTs + open label trials) 3291 pts EU SPC 4.8	Moderate to severe plaque psoriasis candidate for systemic treatment + "high need" subgroup			%	24	41
	ADRs	Hypersensitivity reactions, psoriasis, Arthralgia, psoriatic arthritis, (exacerb./flare) Back pain, asthenia ALT and Ph. Alk increase	ISS (RCTs and all open label trials 3,291 pts EU SPC 4.8	Moderate to severe plaque psoriasis candidate for systemic treatment + "high need" subgroup			%		>1/100 <1/10
	Meningitis aseptic	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		29
	Serious infections including pneumonia, sepsis, cellulitis	Proportion of patients experiencing severe infections	ISS (RCTs and all open label trials 3,291 pts	Moderate to severe plaque psoriasis candidate for systemic treatment + "high need" subgroup			%/100 pt-yrs	1.4	2.8
	Opportunistic infections including fungal infections, tuberculosis,	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		111

Name	Description	Source	Patient population	Fixed Lower†	Fixed Upper†	Units	Placebo (pts number)	Efalizumab 1mg/kg/wk (pts number)
herpes virus infections, EBV, CMV								
Serious thrombo cytopenia	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		70
Immune haemolytic anemia	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		24
Psoriasis severe forms (erythrodermic, pustular)	Number of cases	ISS (RCTs and all open label trials 3,291 pts	Moderate to severe plaque psoriasis candidate for systemic treatment + “high need” subgroup			%	1.4	3.2
Nervous System disorders including Inflammatory polyradiculopathy, Facial Palsy, GBS, Fisher Miller Syndrome	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		NA
Interstitial lung diseases including lung infiltration,	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		18

Name	Description	Source	Patient population	Fixed Lower†	Fixed Upper†	Units	Placebo (pts number)	Efalizumab 1mg/kg/wk (pts number)
pulmonary fibrosis								
Serious cases of psoriasis exacerbation or rebound		PSUR 10	Cumulative post-mkt data 47,000 pt/yrs			No		390 (0.8/100 pt-years)
Brain infections including Encephalitis and PML	Number of cases	PSUR 10	Cumulative post-mkt data 47,000 pt/yrs (5,900-8,900 >2 years)			No		8 (4 PML)