Lead team presentation

Pegaspargase for Acute Lymphoblastic Leukaemia– STA

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Lead team: Gail Coster & Judith Wardle

ERG: Kleijnen Systematic Reviews

Summary of evidence and key issues

Clinical effectiveness

Paediatric population:

- Favourable results for PEG. vs. E Coli (meta-analysis)
- Favourable results for E coli vs. Erwinia (2 studies)

Adult population

- No comparative studies

Cost effectiveness

Company's base case: In the paediatric and adult populations, PEG.>Erwinia either dominates the other sequences or has an ICER in SW quadrant of the CE plane

ERG's base case: In the whole population PEG> Erwinase dominates the other sequences

Uncertainty:

- Limited comparative evidence available
- The effectiveness of the lower dose of PEG. (1,000 IU/m^2
- Is treatment sequencing a valid approach?
- Does the economic model reflect clinical practice?
- Hypersensitivity rates for modelling
- Is it appropriate to assume equal effectiveness between the 3 asparaginase treatments?

Pegaspargase for ALL

Equality issues raised

- Rare form of cancer
- Presents primarily in children, adolescents and young adults: ~75 % diagnosed are under 25 years of age
- If NICE does not give approval, UK children will be the only children among developed countries not to have access

Innovation

Now standard of care for 1st line asparaginase treatment for all patients with ALL

Disease background

- Acute form of cancer of the white blood cells
- Rare - 0.2% of new cancers in UK
- Predominately disease of childhood but affects adults too
- 54% of cases in UK children aged between 0 – 14 years, highest rates in children ages of 0 – 4 years
- Symptom include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating
- Currently no NICE guidance on treatment of ALL
- Multi agent chemotherapy generally used and treatment grouped into three main phases:
  - remission – induction
  - intensification / consolidation
  - continuation/ maintenance
- Treatment decisions also take into account patient's disease risk category: low-risk, high-risk, very high-risk & standard risk

Current management

- Asparaginase core component of ALL regimens, most often given during induction and consolidation
- 3 formulations of asparaginase currently available
  - Escherichia coli-derived (E. coli)
  - Erwinia caratovora-derived (Erwinia)
  - polyethylene glycol conjugate of E. coli-derived L-asparaginase (pegaspargase)
- pegaspargase as 1st line treatment driven by UKALL protocols
  - Children, adolescents and young adults: UKALL 2003 & UKALL 2011
  - Adults: UKALL14
- Pegaspargase included in NHS England baseline commissioning since April 2013

Impact on patients and carers (1)

- Patient organisation says that while peak incidence of ALL in children, survival rates decrease with age: 90% for under 14yrs/ less than 15% over 64yrs. So prognosis poor for adults
- Symptom profile is wide: including anaemia, weakness, tiredness, shortage of breath, infections, bleeding & bruising, fever & sweating.
- Non-specific symptoms mean diagnosis in 64% is made on emergency admission
- Huge emotional impact of diagnosis on whole family as well as the patient

Impact on patients and carers (2)

- Key patient/family goal is survival but QoL also very important
- Pegaspargase is better tolerated than other options & effect lasts longer so fewer injections needed. Less hypersensitivity so safer
- Since pegaspargase (+ other chemo) is already standard of care, this is unusual appraisal: rejection by NICE would be step backwards for clinical practice

Pegaspargase

- Marketing authorisation: Pegaspargase for the treatment of ‘acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients (Jan 2016).
- Mode of administration: Intramuscular or intravenous infusion
- Dosage:
  - SmPC recommends 2,000-2,500 IU/m^2
  - Clinical practice 1,000 IU/m^2 based on the UKALL protocols

Company decision problem (1)

	NICE scope	Company's decision problem	
		Same as NICE scope?	Company comment
Population	Patients with ALL	×	Pegaspargase 1st line - UKALL protocols. Therefore patient populations are children and adults with newly-diagnosed ALL
Intervention	Pegaspargase plus standard chemotherapy	✓	But (economic model 1,000 IU/m2)

Company decision problem (2)

	NICE scope	Company's Decision problem	
		Same as NICE scope?	Company comment
Comparator(s)	Non-pegylated forms of: • E. coli-derived plus standard chemotherapy • Erwinia derived plus standard chemotherapy	✓	N/A

Company decision problem (3)

	NICE scope	Company's decision problem	
		Same as NICE scope?	Company comment
Outcomes	• Overall survival • Progression free survival • Treatment response rates • Event free survival • Asparaginase activity • Adverse effects of treatment • Health related quality of life	✓	Event free survival was used in many studies and this outcome will incorporate progression free survival

Clinical trial design (1): Paediatric population

- Company submission focusses on 2 main studies: CCG-1962 and UKALL2003

	CCG-1962	UKALL2003
Population	Children aged 1-9 years with standard risk ALL	Consecutive children and young adults ages 1-24 years with ALL Clinical standard and intermediate risk patients were eligible
Design	Multicentre, randomised, open-label, Phase III Randomised 1:1 (method of randomisation not stated) 8 centres in the US (children's hospitals and clinics)	Multicentre, randomised, open-label Radomisation 1:1 (method of randomisation stated) 45 centres in the UK and Ireland.

Clinical trial design (2): Paediatric population

	CCG-1962	UKALL2003
Trial drugs	• Induction (4 weeks) • Consolidation (4 weeks) • Two 8 week DI phases • Maintenance therapy At start of induction, patients randomly assigned to receive either • pegaspargase 2500 IU/m^2 IM on day 3 of induction and each DI phase • Native asparaginase 6000 IU/m^2 IM 3 times per week, for 9 doses in induction and 6 doses in each DI phase	• Induction (4 weeks) • Consolidation (4-9 weeks) • 2 interim maintenance phases (8 weeks) • 2 DI phases (7 weeks) • Continuing therapy Patients received 1 of 3 escalating-intensity treatment regimens (designated A, B, and C respectively) depending on clinical risk group Each regimen included treatment with pegaspargase 1000 IU/m^2 IM. All regimens included low doses at induction on days 4 and 18

Clinical trial design (3): Paediatric population

	CCG-1962	UKALL2003
Duration of study	Treatment duration for girls 2 years, boys 3 years Enrollment between May 1997 and Nov. 1998	Treatment duration for females 2 years, males 3 years, from the start of interim maintenance Enrollment between Oct. 2003 and June 2011
Primary outcomes	• EFS (included: induction death, no induction response, relapse at any site, second malignant neoplasm • Incidence of high-titre asparaginase antibodies in DI no.1	• EFS defined as time to relapse, secondary tumour, or death • OS defined as time to death

Trial Results (1): Paediatric population CCG-1962

Asparaginase antibody formulation

Chemotherapy Phase	Native asparaginase mean ratio SEM (n) ±	Pegaspargase mean ratio SEM (n) ±	P-value
Induction	2.3 ± 0.9 (47)	1.3 ± 0.2 (41)	NS
DI no.1	3.0 ± 0.7 (43)	1.9 ± 0.8 (47)	p=0.01‡
DI no.2	2.1 ± 0.6 (45)	2.1 ± 0.8 (45)	NS

Source: Table 13, page 63 company submission

Trial Results (2): Paediatric population CCG-1962

Event free survival

Event free survival	Native asparaginase % (95% C.I.)	Pegaspargase % (95% C.I.)
3-year EFS	79 (68-90)	83 (73-93)
5-year EFS	73 (61-85)	78 (67-88)
7-year EFS	66 (52-80)	75 (63-87)

Source: Table 13, page 63 company submission

Trial Results (3): Paediatric population UKALL2003

	Whole population	Low risk population		High risk population	
		Standard treatment	Reduced treatment	Standard treatment	Augmented treatment
EFS 5 years % (95% C.I.)	87.2 (85.8-88.6)	95.5 (92.8-98.2)	94.4 (91.1-97.7)	82.8 (78.1-87.5)	89.6 (85.9-93.3)
OS 5 years % (95% C.I.)	91.5 (90.0-92.7)	98.5 (96.9-100)	97.9 (95.3-100)	88.9 (85.0-92.8)	92.9 (89.8-96.0)
Risk of relapse 5 years % (95% C.I.)	8.85 (7.8-10.0)	2.4 (0.2-4.6)	5.6 (2.3-8.9)	14.2 (9.7-18.7)	7.5 (4.2-10.8)

Meta-analysis: Paediatric population

- Company reported results of a meta-analysis of 39 studies

- Company considered studies too heterogeneous to conduct an Indirect Treatment Comparison

Clinical trial design and results (1): Adult population

	Douer (2007)	Douer (2014)	Wetzler (2007)
Population	Adults aged 55 years or younger with newly diagnosed ALL	Adults aged 18–57 years with newly diagnosed ALL	Adults with untreated ALL
Study Objectives	To establish the remission rate in adults who received pegaspargase	To establish the remission rate in adults who received pegaspargase To establish rates of disease free survival (DFS) and OS	To compare the rate of DFS and OS in adults who received pegaspargase and had asparagine depletion compared with adults without asparagine depletion

Clinical trial design (2): Adult population

	Douer (2007)	Douer (2014)	Wetzler (2007)
Design	Interventional, prospective, non-randomised study (n=25)	Interventional, prospective, non-randomised study (n=51)	Interventional, prospective, non-randomised study (n=85)
Results	After 1 dose of pegaspargase, 90% had complete remission	After the 1st induction phase of treatment: 96% had complete remission, DFS 58% and OS 51% after 7 years follow-up	After the induction and intensification phase of treatment, the patient group without asparaginase depletion had a lower rate of • DFS: HR 2.21 (95% C.I. 1.19-4.13) • OS: HR 2.37 (95% C.I. 1.38 to 4.09)

Adverse events overview

- The adverse events observed with pegaspargase were consistent with those expected of asparaginase.
- Most common Grade 2 or higher adverse reactions at doses of 2000-2500 IU/m^2 included anaphylactic reaction, febrile neutropenia, anemia, hyperglycemia, decreased platelet count, decreased neutrophil count and increased bilirubin levels

Evidence Review Group's critique (1)

- The ERG stated that it disagreed with the company that CCG-1962 and UKALL2003 were the most important trials to assess the clinical effectiveness of pegaspargase
  - It identified 7 RCTs in the company's searches which it considered relevant for the appraisal, 5 RCTs comparing pegaspargase with E. coli derived asparaginase, and 2 RCTs comparing E. coli derived asparaginase with Erwinia derived asparaginase (see slides 22 & 24)
- The ERG agreed with the company that there was no evidence to conclude that there was a difference in the clinical effectiveness of pegaspargase and E.Coli derived asparaginase. However, the ERG stated that it was unclear whether this was because of a lack of evidence or lack of a difference in effect
  - None of the included RCTs was powered to assess equivalence and it was not possible to pool results from different studies.

Additional studies* (1): Paediatric population Pegaspargase vs. E coli

Study	Population Age (years)	Pegaspargase %	E.coli %	Diff. %
EFS at 5 years				
CCG-1961	1 to 21	81.2 (SD 2.4)	71.7 (SD 2.7)	9.5
DFCI-91-01	1 to ≤18	78.0 (SD 4.0)	84.0 (SD 4.0%)	6.0
DFCI-ALL 05-001	1 to18	90.0 (95% C.I. 86.0 to 94.0)	89.0 (95% C.I. 85.0 to 93.0)	1.0
OS at 5 years				
CCG-1961	1 to 21	88.7 (SD 1.9)	83.4 (SD 2.2)	5.3
DFCI-ALL 05-001	1 to 18	96.0 (95% C.I. 93.0 to 98.0)	94.0 (95% C.I. 89.0 to 96.0)	2.0

*Identified by ERG from the company's searches as relevant

Additional studies*(2): Paediatric population Erwinia vs. E.coli

Study	Population Age (years)	Erwinia %	E.coli %	Diff. %
EFS at 10 years				
DFCI-95-01	0 to 18	75.2 (SE 3.8)	84.6 (SE 3.4)	0.4
EFS at 6 years				
EORTC-CLG 58881	0 to 18	59.8 (SE 2.6)	73.4 (SE 2.0)	6.0
OS at 10 years				
DFCI-95-01	0 to 18	75.2 (SE 3.8)	84.4 (SE 3.4)	9.2
OS at 6 years				
EORTC-CLG 58881	0 to 18	75.1 (SE 2.3)	83.9 (SE 2.0)	8.8

* Identified by the ERG from the company's searches as relevant

Evidence Review Group's critique (2)

- The ERG highlighted that the UKALL protocols use a dose of 1,000 IU/m^2 for pegaspargase. However:
  - The SmPC recommended dose is higher (2,000-2,500 IU/m^2)
  - No comparative evidence for the lower dose of pegaspargase versus other types of asparaginase. All trials comparing pegaspargase with E. coli derived asparaginase compared 2,500 IU/m^2 pegaspargase with 6,000 IU/m^2 E coli derived asparaginase
  - No head-to-head comparison of pegaspargase used at 1,000 IU/m^2 and 2,500 IU/m^2 doses
- None of the studies in the adult population included a control group. The ERG considered that these studies provided no evidence for the relative effectiveness of pegaspargase compared with other asparaginases

Key issues for consideration

- Are the results from the comparative studies available for pegaspargase (2,500 IU/m^2) generalisable to UK clinical practice where pegaspargase 1,000 IU/m^2 is given?
- Is there sufficient evidence available to assume equal effectiveness between pegaspargase, native E. coli derived asparaginase and Erwinia-derived asparaginase in the paediatric or adult populations?

Lead team presentation Pegaspargase for treating acute lymphoblastic leukaemia-STA

1st Appraisal Committee meeting

Cost Effectiveness

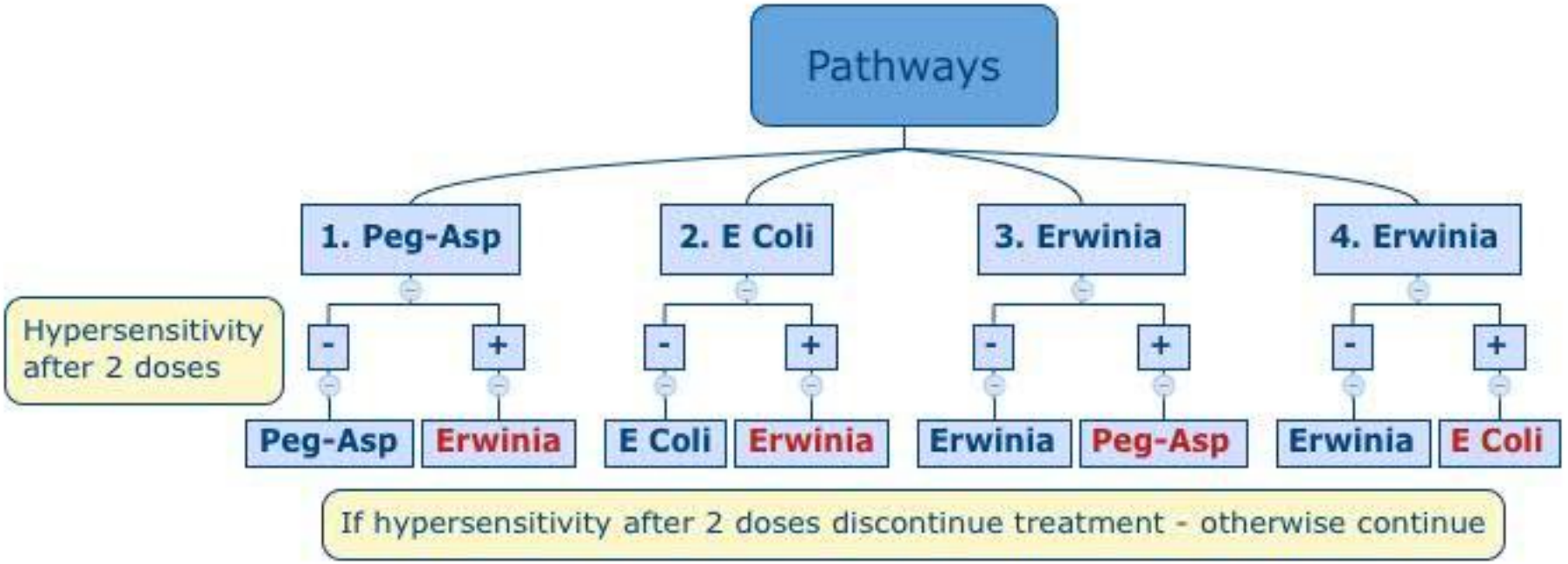
Lead team: Rachel Elliott

ERG: Kleijnen Systematic Reviews

15th June 2016

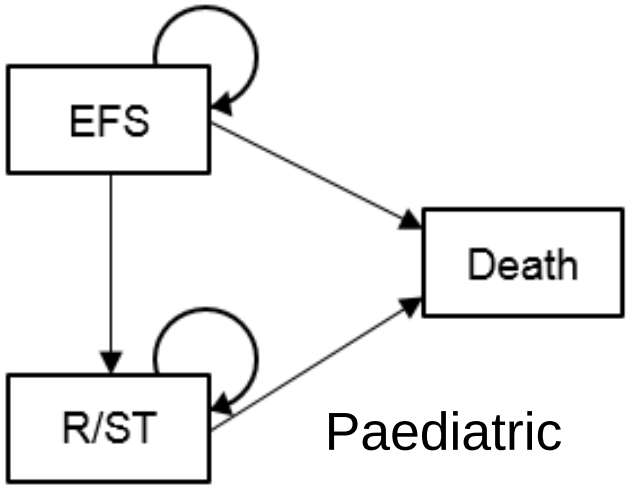
Company: Model and decision tree structure

- Combination of a decision tree and health state transition Markov model
- Decision tree modelled patient flow during treatment administration:

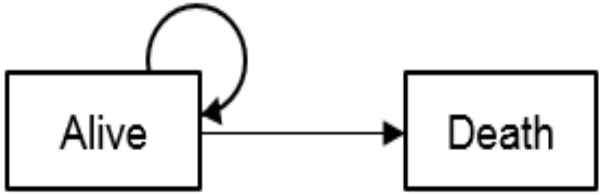


Company: Markov model structure

- accounted for potential relapse/secondary tumour (R/ST) and death
- extrapolates beyond the time horizon of the clinical trials (5 years)



Paediatric



Adult

NHS and PSS perspective; Cycle length post treatment: 1 year; Time horizon: lifetime; EFS: event-free survival; R/ST, relapse/secondary tumour

R/ST health state not considered in adults, EFS and OS assumed to be the same.

Company: Paediatric model structure

- Children and young people newly diagnosed with ALL treated with pegaspargase as an initial 1st line treatment (paediatric population)
- Aged ≤ 25: children, adolescents, young adults from cohort of> 3,200 patients for whom data is available, treated with the UKALL 2003 protocol
  - Risk stratification high-risk (HR), intermediate-risk (IR) and standard-risk (UKALL 2003 protocol)
- Cancer Research UK (CRUK) data, of the new ALL cases diagnosed p.a. in those aged 0-65, 74.4% <25 years old
  - Model median age of 5 years (Vora et al, 2013)

Company: Paediatric model structure (cont.)

	Standard risk	Intermediate risk	High risk
UKALL 2003	NCI standard risk patients aged <16 yrs. with RER	• Patients aged ≥16 yrs. • NCI high risk patients aged <16 yrs. with RER	• Presence of cytogenetic abnormalities • >25% of the marrow made of blasts at day 8 for patients with NCI high risk or at day 15 for patients with NCI standard risk.
UKALL 2011	• NCI standard risk and MRD low • NCI standard risk and RER (if MRD not possible)	• NCI high risk or high risk cytogenetics and MRD low • NCI high risk or high risk cytogenetics and RER (if MRD not possible)	• MRD high • SER (if MRD not possible)

RER = rapid early response (<25% blasts at day 8 for patients with NCI high risk and <25% blasts at day 15 for patients with standard risk), SER = slow early response (>25% at day 8 or day 15 for high and standard risk patients, respectively), MRD low = < 0.005% at day 29 inductions

Company: Adult model structure

- Adults aged 26-65 years with pegaspargase at any stage of the treatment pathway (adult population)
- Within this group, a further split is made between those aged ≤ 40 and aged ≥ 41and those eligible, or not, for transplant
- Mean age of the adult population
  - 31.2 years (26-40 age group)
  - 52.6 years (41-65 age group)
- Patients not included in the company submission:>65 years, relapsed patients (neither routinely receive pegaspargase)

Company: Model assumptions

- Concomitant medications would remain unchanged
- 6 E.coli asparaginase and Erwinase doses correspond to 1 of pegaspargase
- Only a difference in the occurrence of hypersensitivity between different asparaginase formulations
- Risks of hypersensitivity the same for both paediatric and adult populations
- Hypersensitivity occurring at 2nd injection
- In Adults, EFS and OS assumed to be the same

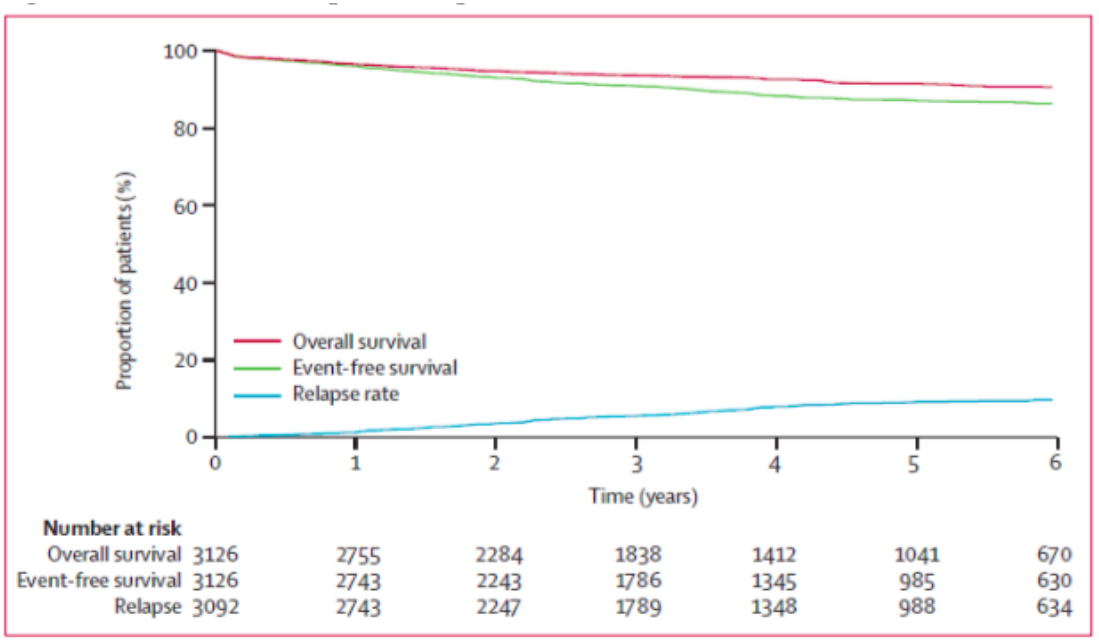
Company: Overview of asparaginase treatment during the complete ALL treatment course

Paediatric population	**Ind**	**Cons**	**IM 1**	**DI 1**	**IM 2**	**DI 2**	**Cont.**
High risk	1w	6w	15w	23w	31w	39w	47w
Intermediate risk	1w	6w	11w	19w	26w	34w	41w
Standard risk	1w	6w	9w	17w	24w	32w	39w
Adult population	**Ind**	**Int.**	**Cons cycle 1**	**Cons cycle 2**	**Cons cycle 3**	**Maint**	
≤40 years	1w	9w	13w	16w	19w	25w	
≥41 years	1w	9w	13w	16w	19w	25w	

Green cells: treatment phases during which asparaginase is administered.
Cons: Consolidation, Cont: continuation, DI: delayed intensification, IM: interim maintenance, Ind: Induction, Int: Intensification, Maint: Maintenance

Company: Paediatric event-free and overall survival

- From the results of the UKALL 2003 trial
- Outcomes presented for the 3 risk groups:
  - 5 year OS: 95%, 90% and 80% for SR, IR, and HR groups, respectively
  - 5 year EFS: 90%, 85% and 75% for SR, IR and HR groups, respectively
- Discontinuation due to hypersensitivity:
  - $OS_{(hyper)} = 0.95 \times OS$



Company: Adult event-free and overall survival

- OS from UKALL14 protocol adult patients
- In the model: 5 year OS:
  - Adults >41 years old: 30%
  - Adults ≤40 years old: 40%
- Weibull distribution assumed
- OS at 40 years: 0%
- OS ≡ EFS (expert opinion)

- Discontinuation due to hypersensitivity:
  - $OS_{(hyper)}$ = 0.95 X OS

Company:Health states and utility values (relative utility decrement per treatment phase (Furlong et al.)

Population norms				
HUI2	0.95			
HUI3	0.92			
ALL treatment phase	**Ind.**	**CNS**	**Int.**	**Cont.**
HUI2	0.74	0.82	0.86	0.88
HUI3	0.67	0.75	0.79	0.85
Relative utility decrement				
HUI2	22%	14%	9%	7%
HUI3	27%	18%	14%	8%
Average	**25%**	**16%**	**12%**	**7%**

Ind., induction; CNS: central nervous system; Int., intensification; Cont., continuation.

Company: Utility decrements applied in the model

Paediatric	**Ind.**	**Cons**	**IM 1**	**DI 1**	**IM 2**	**DI 2**	**Cont.**	**End week**
	25%	16%	12%	12%	12%	12%	7%	0%
Adults	**Ind.**	**Int.**	**Cons. 1**	**Cons. 3**	**Maint.**	**End week**		
	25%	25%	12%	12%	7%	0%		

Ind., induction; Int., intensification; IM, interim maintenance; DI, delayed intensification; Cons., consolidation; Cont., continuation; Maint, maintenance.

- Utility decrements subtracted from age-specific EQ-5D population norms (Szende et al.)
- Assumed that the reported EQ-5D utility corresponded with the utility at the median age of each age group.
- For all other ages, a logistic regression was used to interpolate between the observed utility values
- Utility decrement for hypersensitivity: 0.014 (from NICE clinical guideline for anaphylaxis [CG 134])

Company: Resources and costs

- Drug acquisition and administration costs
  - Estimated treatment administration cost of £163 based 30 mins administration and 60 mins monitoring by a band 6 nurse.
- Costs associated with administration of hypersensitivity reactions to treatment
  - £470.00 (NICE CG134 Anaphylaxis Costing Statement 2011)
- Scenario analysis varied the cost of a hypersensitivity reaction to pegaspargase from £72 (the lowest estimate in CG134) to £611 (the highest estimate in CG134)
- No other costs were included in the model

Company: Resources and costs

	Dose (UI/m^2)	Ave. BSA (m^2)	Ave. dose per patient	Vial size	Vials per dose	Costs per Vial	Admin cost per dose	Drug cost per dose
Paediatric								
PEG.	1,000	0.75	750	3,750	1	1,296.19	163.50	1,296
E coli	10,000	0.75	7,500	10,000	1	70.87	163.50	71
Erwinase	20,000	0.75	15,000	10,000	2	613.00	163.50	1,226
Adult								
PEG.	1,000	1.79	1790	3,750	1	1,296.19	163.50	1,296
E coli	10,000	1.79	17,900	10,000	2	70.87	163.50	142
Erwinase	20,000	1.79	35,800	10,000	4	613.00	163.50	2,452

Company: Resources and costs (cont.): Disaggregated costs per cost category

Item	Average treatment cost			
	PEG. > Erwinase	**E coli > Erwinase**	**Erwinase > PEG.**	**Erwinase>E coli**
Technology cost	**£6,980**	**£7,716**	**£43,348**	**£43,076**
PEG.	£6,650	£0	£399	£0
E coli	£0	£2,144	£0	£127
Erwinase	£330	£5,571	£42,949	£42,949
Administration cost	**£878**	**£4,769**	**£4,857**	**£5,039**
PEG.	£839	£0	£50	£0
E coli	£0	£4,145	£0	£233
Erwinase	£40	£625	£4,807	£4,807
Hypersensitivity	£12	£127	£29	£34
Total	**£7,871**	**£12,612**	**£48,234**	**£48,149**

Company's base case results for whole population (combines paediatric and adult populations)

Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG. > Erwinase	7,871	17.3431	—	—	—
E coli > Erwinase	12,612	17.2926	-4,741	0.0504	-94,029
Erwinase > E coli	48,149	17.3396	-40,277	0.0035	-11,541,184
Erwinase > PEG.	48,234	17.3477	-40,362	-0.0047	8,627,243

Abbreviations: ICER, incremental cost-effectiveness ratio; PEG, pegaspargase; QALYs, quality-adjusted life years

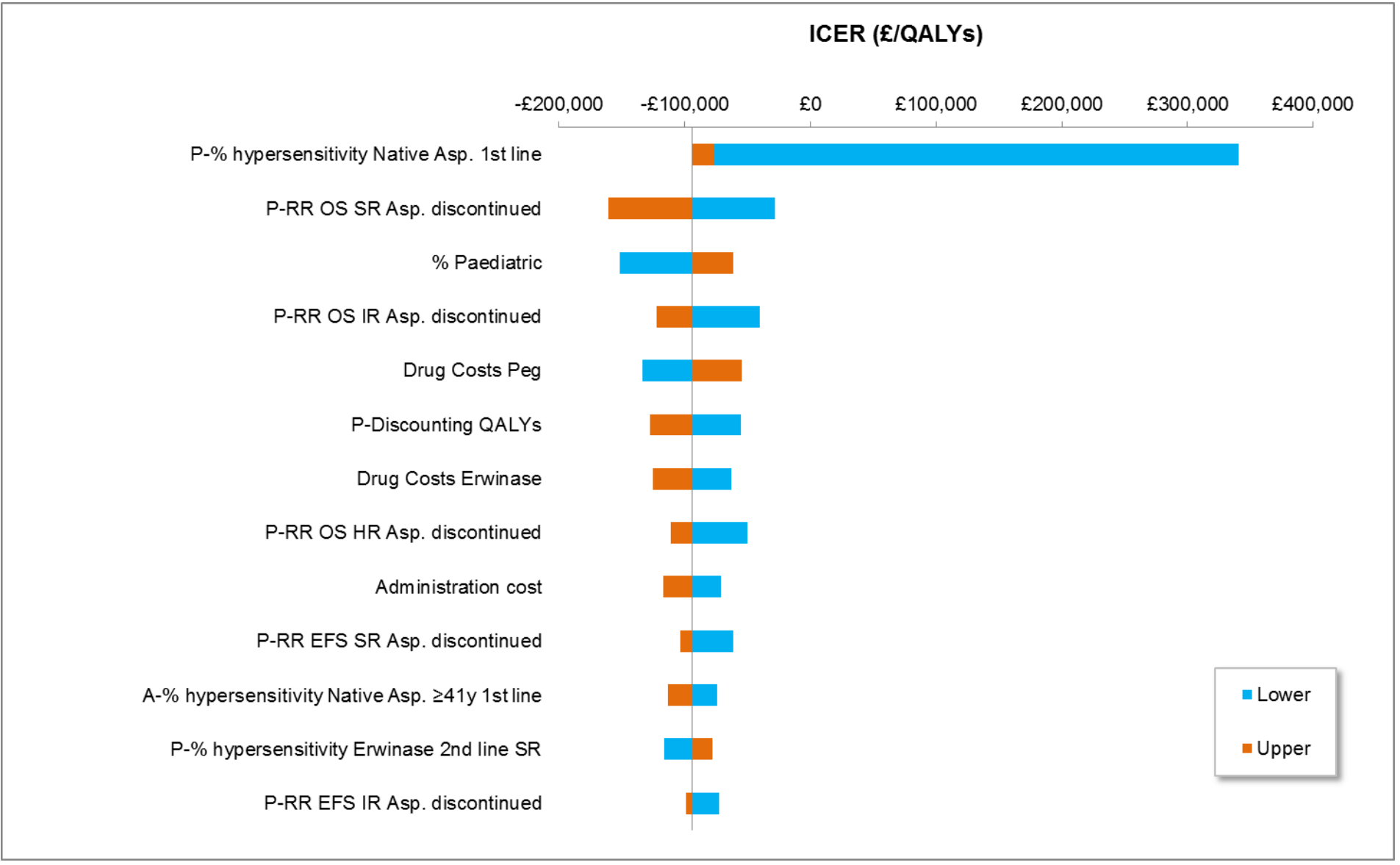
Company's base case results

Paediatric population					
Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG. > Erwinase	8,545	22.1294	—	—	—
E coli > Erwinase	12,352	22.0633	-3,807	0.0662	Dominant
Erwinase > E coli	44,781	22.1248	-36,236	0.0046	Dominant
Erwinase > PEG.	44,900	22.1356	-36,355	-0.0061	5,917,762

Adult population					
Technologies	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
PEG. > Erwinase	5,913	3.4327	—	—	—
E coli > Erwinase	13,368	3.4280	-7,455	0.0047	Dominant
Erwinase > E coli	57,936	3.4324	-52,023	0.0003	Dominant
Erwinase > PEG.	57,922	3.4332	-52,010	-0.0004	123,446,241

Abbreviations: ICER, incremental cost-effectiveness ratio; PEG, pegaspargase; QALYs, quality-adjusted life years

Company's deterministic sensitivity analyses: results



Company's scenario analysis: results (cont.)

Scenario	PEG. > Erwin vs. E coli > Erwin	PEG. > Erwin vs. Erwin > PEG.	PEG. >Erwin vs. Erwin > E coli
Base case	Dom	£8.7m*	Dom
100% paediatric pop.	Dom	£5.9m*	Dom
100% adult pop.	Dom	£123.6m*	Dom
Min cost hyper.	Dom	£8.7m*	Dom
Max cost hyper.	Dom	£8.7m*	Dom
Min rate hyper.	Dom	Dom	Dom
Max rate hyper.	Dom	£2.1m*	Dom
1.5% disc rate (paed)	Dom	£5.1m*	Dom
PEG dose per SmPC	Dom	£8.6m*	Dom
Min cost E Coli	Dom	£8.7m*	Dom
Max cost E Coli	Dom	£8.7m*	Dom
Mean paed age =1	Dom	£8.6m*	Dom
Mean paed age = 18	Dom	£9.5m*	Dom
Best case EFS/OS	Dom	£84,914*	£86,810*
Worst case EFS/OS	£20,326*	£49,501*	£50,070*

Abbreviation: Dom; Dominant

* South West Corner

Company's cost minimisation analysis: PEG.>Erwinase vs. E coli>Erwinase

	Incremental costs	Incremental QALYs	ICER
Cost Minimisatiion	-£354	0.00	NA

Assuming that pegasparagase, E coli and Erwinase are equivalent in terms of OS and EFS

Evidence Review Group (ERG) comments

- Correction of errors in the model:
  - risk distribution in paediatric patients; background mortality; same number of administrations in case of hypersensitivity; utility after stopping treatment
- Adjustments to the model
  - Mean age instead of the median age in the paediatric model
  - No second interim maintenance and delayed intensification course.
  - Risk of hypersensitivity to Peg based on % patients switching treatment.
  - Risk of hypersensitivity to Erwinase similar for 1st and 2nd line treatment and based on % patients switching asparaginase treatment.
  - Different OS and EFS estimates for the 3 paediatric risk groups.
  - Allow the OS and EFS to vary independently in the PSA
  - Change relative reduction in OS for patients who discontinue asparaginase due to hypersensitivity to 2 different formulations
  - Change mortality risk for patients in the R/ST state
  - Change timing of the different treatment phases
  - Change standard errors used in the PSA

ERG's exploratory analyses: deterministic base case - Whole population

Treatment					ICER (£)
	Costs (£)	QALYs	Cost (£)	QALYs	
PEG. > Erwinase	7,329	17.5787	-	-	—
E Coli > Erwinase	11,083	17.5607	-£3,754	0.02	Dominant
Erwinase > PEG.	35,513	17.5787	-£28,184	0.00	Dominant
Erwinase > E coli	35,447	17.5608	-£28,118	0.018	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; PEG, pegaspargase; QALYs, quality-adjusted life years

Revised ERG base case, incorporating corrections and amendments (1)

Scenario	
1	Corrections in model
2	Mean instead of median age paediatric population
3	No 2nd interim maintenance and delayed intensification course & correction timing treatment
4	Hypersensitivity rate PEG. 13.2%
5	Hypersensitivity rate Erwinase 9%
6	OS estimate based on UKALL 2003
7	EFS estimate based on UKALL 2003
8	Reduction of OS and EFS in case of discontinued asparaginase = 19%
9	Yearly mortality rate in R/ST state = 35%
10	ERG Base-case

Revised ERG base case, incorporating corrections and amendments (2)

	PEG. >Erw vs. E coli >Erw			PEG.>Erw vs. Erw>PEG			PEG. >Erw vs. Erw>E coli		
	Costs	QALY	ICER	Costs	QALY	ICER (£)	Costs	QALY	ICER (£)
Base	-4,741	0.050	Dom	-40,362	-0.005	*~8.6m**	-40,277	0.003	Dom
1	-4,384	0.051	Dom	-37,218	-0.005	*~7.9m**	-37,142	0.004	Dom
2	-4,741	0.050	Dom	-40,362	-0.005	*~8.7m**	-40,277	0.003	Dom
3	-3,980	0.050	Dom	-32,768	-0.005	*~7.0m**	-32,705	0.003	Dom
4	-3,096	0.019	Dom	-38,688	-0.031	*~1.3m**	-38,632	-0.028	*~1.4m**
5	-7,022	0.012	Dom	-39,048	0.000*	Dom	-38,920	0.012	Dom
6	-4,741	0.052	Dom	-40,362	-0.005	*~8.3m**	-40,277	0.004	Dom
7	-4,750	0.051	Dom	-40,451	-0.005	*~8.5m**	-40,366	0.004	Dom
8	-4,741	0.192	Dom	-40,363	-0.018	*~2.3m**	-40,278	0.013	Dom
9	-4,741	0.049	Dom	-40,362	-0.005	*~ 9.0m**	-40,277	0.003	Dom
10	**-3,754**	**0.018**	**Dom**	**-28,184**	**0.000***	**~**2.5m*	**-28,118**	**0.018**	**Dom**

ERG's exploratory analyses: scenario analysis – Whole Population (1)

Scenario	
1	Dosage of pegaspargase 2,500 IU/m^2
2	Best-case scenario with better EFS and OS for pegaspargase
3	Worst-case scenario with worse EFS for pegasparagase
4	Quality of life utilities based on algorithm to map HU13 on EQ-5D
5	Change utility decrement for the R/ST health state
6	Apply 4 doses of E coli or Erwinase for each dose of pegaspargase

ERG's exploratory analyses: scenario analysis – whole population (2)

	PEG. >Erwinase vs E coli >Erwinase			**PEG. >Erwinase vs Erwinase >Peg.**			**PEG. >Erwinase vs Erwinase>E. coli**		
Scenario	Costs	QALY	ICER	Costs	QALY	ICER	Costs	QALY	ICER
Base	**-4,099**	**0.02**	**Dom.**	**-28,526**	**0.01**	**Dom.**	**-28,462**	**0.02**	**Dom.**
1	-3,306	0.02	Dom.	-27,842	0.01	Dom.	-27,670	0.02	Dom.
2	-4,039	1.45	Dom.	28,309	1.45	Dom.	-28,244	1.45	Dom.
3	-4,141	-0.86	***4,810****	-28,626	-0.87	***32,907****	-28,562	-0.86	***33,179****
4	-4,099	0.02	Dom.	-28,526	0.01	Dom.	-28,462	0.02	Dom.
5	-4,099	0.02	Dom.	-28,526	0.01	Dom.	-28,462	0.02	Dom.
6	739	0.02	**36,499¶**	-17,213	0.01	Dom.	-17,155	0.02	Dom.

Abbreviation: Dom; dominant

**** South West Corner***

¶ North East Corner

Potential equality issues

- Consultees and commentators submissions:
  - ALL is an orphan disease.
  - ALL is unusual in that the peak incidence is in children (aged <14). As such, any decision not to recommend pegaspargase would have a disproportionate impact on children.
  - If NICE does not give approval, UK children with ALL will be the only children among developed countries not to have access

Innovation

- The company stated that it considered to be innovative as it has become the standard of care for 1st line asparaginase treatment for people with ALL of all ages
- How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?
- Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?

Key cost effectiveness issues for consideration

- Is treatment sequencing a valid approach to modelling?
- Does the company's economic model reflect clinical practice in England?
- How robust are the inputs into the economic model?
- Is it appropriate to use the rates of hypersensitivity to reflect the proportion of patients who require a treatment switch as a result of hypersensitivity?
- Is it appropriate to assume equal effectiveness between pegaspargase, E. coli derived asparaginase and Erwinia-derived asparaginase?
- Are there any potential equality issues?
- Does the committee have any comments about Innovation?
- Is there a case for inclusion in the CDF?
- Has the Committee heard anything that would change the conclusion in the NICE position statement on the PPRS?

The southwest corner of the cost effectiveness plane