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Cost effectiveness analysis of rifaximine for the prevention of encephalopaty relapses in France

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RIFAXIMIN
FOR TREATING HEPATIC ENCEPHALOPATHY

Incidence, prevalence and natural history of the disease

- Hepatic encephalopathy is a complex neuropsychiatric syndrome arising the most during acute or chronic liver failure.
- It is one of the most severe complications of liver cirrhosis
- **One year mortality** after the disease onset is close to 40%
- **700 000 patients** suffer from liver cirrhosis in France (Inserm, 2012)
- Among them 30% are classified as severe and could develop a complication (including HE).
- Cost of medical care was estimated at **40 millions euros** in 2013.

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Stages of Hepatic Encephalopathy

– Two forms of HE are recognized:

- patients with **minimal** or **covert hepatic encephalopathy**(**CHE**)
- and those with **clinically relevant or overt hepatic encephalopathy (OHE).**
- **After an overt episode**, patients usually **return to be unimpaired** or to a covert state of HE, and this is considered to constitute a state of remission

Current treatments of HE

- The current standard of care for patients with HE is a treatment with lactulose [Bass *et al.* 2010].
- Maharshiet *al.* 2015; Paik *et al.* 2005; Sidhu *et al.* 2015).have reported rifaximin-α to be more efficacious than lactulose in the treatment of HE [
- [Sanyal *et al.* 2011] study demonstrated significant improvements in the HRQoL of patients in remission in the rifaximin-α group compared with those in the placebo group
- A phase III study [Bass *et al.*2010] demonstrated that rifaximin-α plus concomitant lactulose therapy (over a 6-month period as compared with placebo plus concomitant therapy) had significantly reduced the risk of an episode of OHE and the risk of hospitalization due to OHE.

Objectives of the study

- The study aim was to estimate the long-term cost effectiveness of rifaximin-α (550 mg twice per day) used in combination with standard treatment (lactulose)
- compared with lactulose alone in cirrhotic patients, who have experienced at least two prior OHE events,
- The study was conducted by adopting the point of view of the French national health insurance.

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METHODS

Analytical framework

- **The engine** : a Markov model
- **Includes 4 health states :**
  - Covert states in the model (CHE1 and CHE2) are defined as being equivalent to a Conn score of 0 or 1.
  - Breakthrough episodes of OHE (OHE1 and OHE2) within the model were defined as an increase from Conn score of 0 or 1 to a score of ⩾2;
  - The fifth state was the death state
- **Target Population**: French patients over 18 years old, suffering from liver cirrhosis and having suffered from at least 2 episodes of OHE (mean age=62)
- **Comparators**: rifaximine + lactulose *vs* lactulose
- **Time Horizon**: 2 ; 5 years
- **Cycle duration** : 30.4 days
- **Discount rate** : 4%
- **Results of modelisation**:
  - Efficacy : Quality adjusted life years (QALY), life expectancy (LY)
  - Costs : treatment, disease monitoring

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Clinical pathway

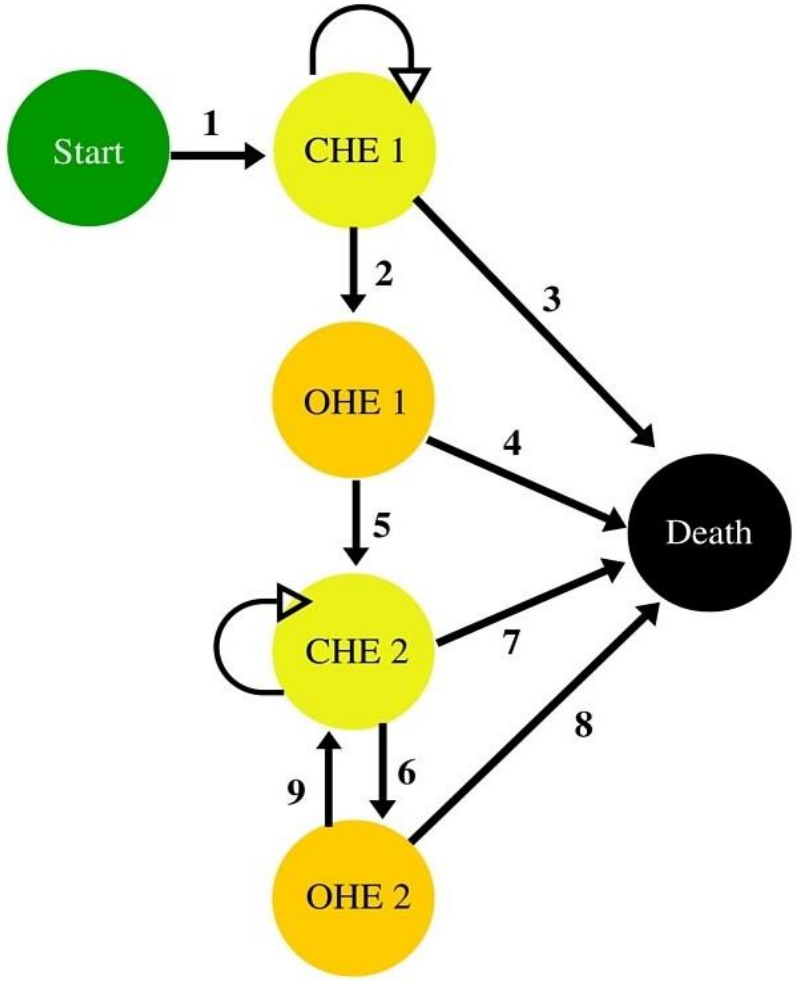
- Patients enter the model in the Cover state (CHE1) [1]
- Then the patients go **from** the Covert State (CHE1) →**to** first-observed Overt episode (OHE1) [2]

  .→or they go to death [3]
- Then the patients go from the Overt state (OHE1]
  → To Covert state (CHE2) [5]

  → to death [4]
- Then the patients go from the Covert state (CHE2]

  →to subsequent Overt episode (OHE2) [6]

  .→to death [7]
- Then the patients go from Overt episode to recovery episode [9] or death [8]



Survival analysis for time-to-event data

- Parametric survival modelling allowed to extrapolate an event-free survival curve beyond the 6-month timeframe of the study.
- Five alternative parametric survival distributions were fitted to the data set based on RFHE3001.
- Loglikelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC) were calculated to determine the best model fit The distribution with the smallest values of model fit statistics is the best fit to the data.
- The techniques used to justify chosen survival modelling methods were: statistical tests, visual inspection,external data, and clinical validity [Diaby *et al.*2014; Latimer, 2013].
- Using this criterion, the choice of the lognormal distribution seems justified. Visual inspection of the five different fits indicates that the lognormal is the best fit of the data.

Main data sources on Efficacy

- RFHE3001 : A 6-month long double blind phase III randomized controlled trial, 299 patients (rifaximin-α n=140 and placebo n=159).

- RFHE3002 : new patients along with patients who did not show an episode of OHE during the RFHE3001 trial.

- Toulouse Study : an observational, retrospective, monocentric study. It includes 62 patients followed during a year : the first 6 months without rifaximin-α and the following 6 months undertaking rifaximin-α.

Cost estimates

- The costs were calculated based on the medical fees recognized by French health insurance. There is no co-pay because HE is classified as ALD 6, which is an aggravation of cirrhosis.
- This analysis incorporates the direct healthcare costs of therapies, doctor visits, hospital visits, diagnostic tests and complications of cirrhosis and HE.
- The costs of therapies were obtained from the public database of drugs.
- The costs of OHE episodes were estimated using the French DRG data base observed in 2014 [Ministère des affaires sociales et de la santé, 2014

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Patient utilities

- Health effects were measured in quality-adjusted life years (QALYs) to capture both survival and quality of life effects associated with treatment.
- For each four model's health states (CHE1, OHE1, CHE2, OHE2) utility score were given
- Analysis of the RFHE3001 [Sanyal et al. 2011] showed that in the covert remission state the rifaximin-α treated patients experienced an incremental improvement in QoL as measured by the Chronic Liver Disease Questionnaire (CLDQ) over those receiving lactulose
- A relationship was derived between disease-specific questionnaire CLDQ and the EQ-5D-3L questionnaire and Remission utility coefficients were estimated
- Utility coefficients were discounted, at 4% rate (HAS recommandation)

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Primary outcome measure

- The key end point for the analysis was the incremental cost-effectiveness ratio (ICER), defined as the incremental cost divided by the number of QALYs saved. incremental cost was the difference in cost between the rifaximin-α arm and the control arm

$$ICER = \frac{\overline{\Delta C}}{\overline{\Delta E}} = \frac{\Delta C_{Rx} + \Delta C_{SE} - \Delta C_{Morb}}{\overline{\Delta QALY's}}$$

$\overline{\Delta C}$ *incremental cost*; $\overline{\Delta E}$ *incremental effectiveness*

ΔC_{Rx} includes all direct medical costs ; $\Delta \dot{C}_{SE}$ includes all direct costs associated with the adverse side effects;ΔC_{Morb} refers to the savings due to the alleviation of disease ; $\overline{\Delta QALY's}$ incremental Quality adjusted life years

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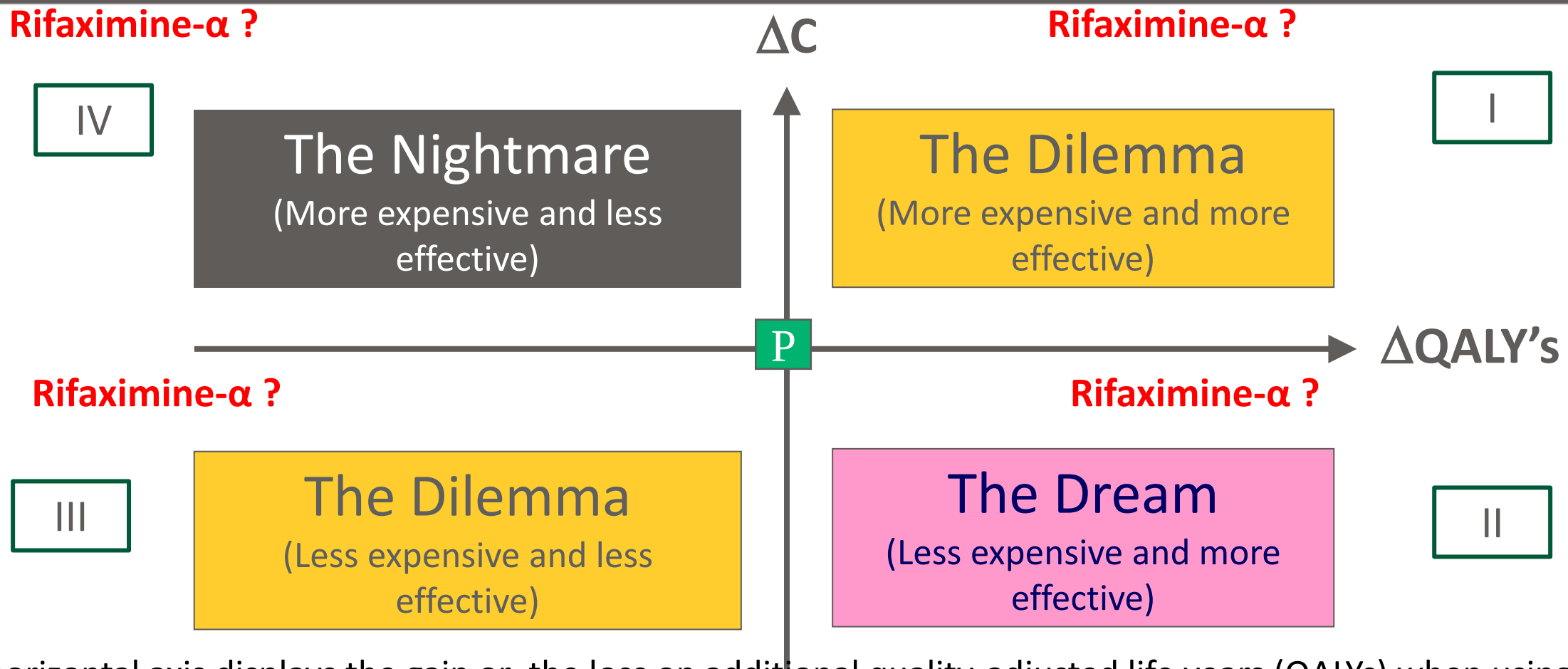
where is Rifaximine-α vs Placebo ? in I; II; II; or IV ?



The horizontal axis displays the gain or the loss on additional quality-adjusted life years (QALYs) when using rifaximin-α instead of placebo, and the vertical axis displays the additional costs or the cost savings with respect to placebo.

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Threshold values for cost effectiveness in health care

Country	Authors	ICER threshold
Explicit ICER threshold range		
UK	NICE	£20 000 - £30 000 per QALY
Implicit ICER threshold values or ranges based on past allocation decisions		
Australia	Henry et al. and the PBAC	AU$69 900 per QALY
New Zealand	Pritchard et al. and PHARMAC	NZ$20 000 per QALY
Canada	Rocchi et al. and the CDR	Range of acceptance: dominant to CAN$80 000 per QALY Range of rejection: CAN$31 000 to CAN$137 000 per QALY
ICER threshold values or ranges proposed by individuals or institutions		
USA	Weinstein	$50 000 per QALY
USA	Braithwaite et al.	$109 000 - $297 000 per QALY
The Netherlands	The Council for Public Health and Health Care	€80 000 per QALY
Canada	Laupacis et al.	CAN$20 000 to CAN$100 000 per QALY
No ICER threshold values or ranges identified		
Finland, Sweden, Norway, Denmark		

CDR: Common Drug Review; NICE: National Institute for Health and Clinical Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; PHARMAC: Pharmaceutical Management Agency.

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Treatments of parametric uncertainties

- **Deterministic Sensitivity Analysis (DSA)**
  - is unidimensional . the value of each variable is changed one by one, while keeping the values of the other variables fixed.
  - The value of each variable was increased and reduced by 20% or 15%; in order to create the tornado diagram
- **Probabilistic sensitivity analysis (PSA)**: takes into account the uncertainty associated with its estimation.

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Method of probabilistic analysis

- For each variable used, we associated **not** **an average probability**, but **a** **distribution of possible values** associated with their occurrence probability.
- For a given family of probability law, we **“lock” the value of its parameters** which best simulates the observed reality.
- After **having specified the distribution law** of each variable, we **draw the realization** of each one of them and the uncertainty **propagate** throughout the model.
- The result of a **probabilistic risk analysis** is a probability distribution.

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RESULTS

Baseline patient characteristics

Variables	values	Sources
Cohort starting age	56	RCT RFHE3001
Lactulose (g) / α-rifaximin (mg) dosage	41.58/1025	Toulouse Study
Lactulose group, lactulose dosage (g)	37,4	Toulouse Study
Monthly cost (lactulose,α-rifaximin) / lactulose	€311.19 / €12.75	
Cost of hospitalization following an episode of CHE	€5,598	PMSI, 2013
6 months number of 0HE episode, lactulose only	2.91	Toulouse Study
6 months number of OHE episode, rifaximin + lactulose	1.03	Toulouse Study
Hospitalization rate for OHE / follow-up time, Lactulose	1.40%	Toulouse Study
Hospitalization rate for OHE / follow-up time, rifaximin	0.96%	Toulouse Study
Mean OHE episode duration (days)	11	RCT RFHE3001
Mean monthly EHE duration (days)	19.44	RCT RFHE3002
Discount rate (coûts et utilités)	4%	HAS
Age-utility adjustment coefficient		King, 1999
Transition distribution extrapolation for 1st CHE episode, rifaximin	Log-normal	RCT RFHE3001
Transition distribution extrapolation for 1st CHE episode, lactulose	log-normal	RCT RFHE3001
Transition distribution extrapolation next CHE episode, rifaximin	log-normal	New patients RFHE3002
Transition distribution extrapolation next CHE episode, Lactulose	log-normal	New patients RFHE3002
Mortality distribution extrapolation in MHE state (CHE1)	log-normal	RCT RFHE3002
Mortality following 1st CHE episode	11.10%	RCT RFHE3002
Mortality adjusting between two episodes of CHE (CHE2)	Weibull	RCT RFHE3002
Mortality after next CHE episode	7.70%	RCT RFHE3002
All cause mortality	Mortality rate	Insee, 2012

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The 5 years Incremental Cost-Effectiveness Ratio

	Lactulose		Rifaximine		ΔQALYs	ΔCoûts	ICER
Time	QALYs	Coûts	QALYs	Coûts			
6 months	0,322	2 259 €	0,336	2 510 €	0,014	252 €	18 247 €
12 months	0,561	3 637 €	0,603	4 419 €	0,042	782 €	18 766 €
18 months	0,775	4 670 €	0,850	6 114 €	0,075	1 444 €	19 184 €
2 years	0,967	5 503 €	1,078	7 639 €	0,111	2 136 €	19 187 €
5 years	1,778	8 555 €	2,094	14 411 €	0,316	5 856 €	18 517 €
10 years	2,478	10 796 €	3,040	20 602 €	0,563	9 806 €	17 430 €

- The results of the study showed the ICER of rifaximin-α in association with lactulose compared with lactulose monotherapy is equal to €18,517 from the base-case analysis over a 5-year lifetime.
- This ICER value means that, by adopting the strategy with rifaximin-α, it costs €18,517 per patient to generate one additional life year gained compared with the lactulose strategy. x

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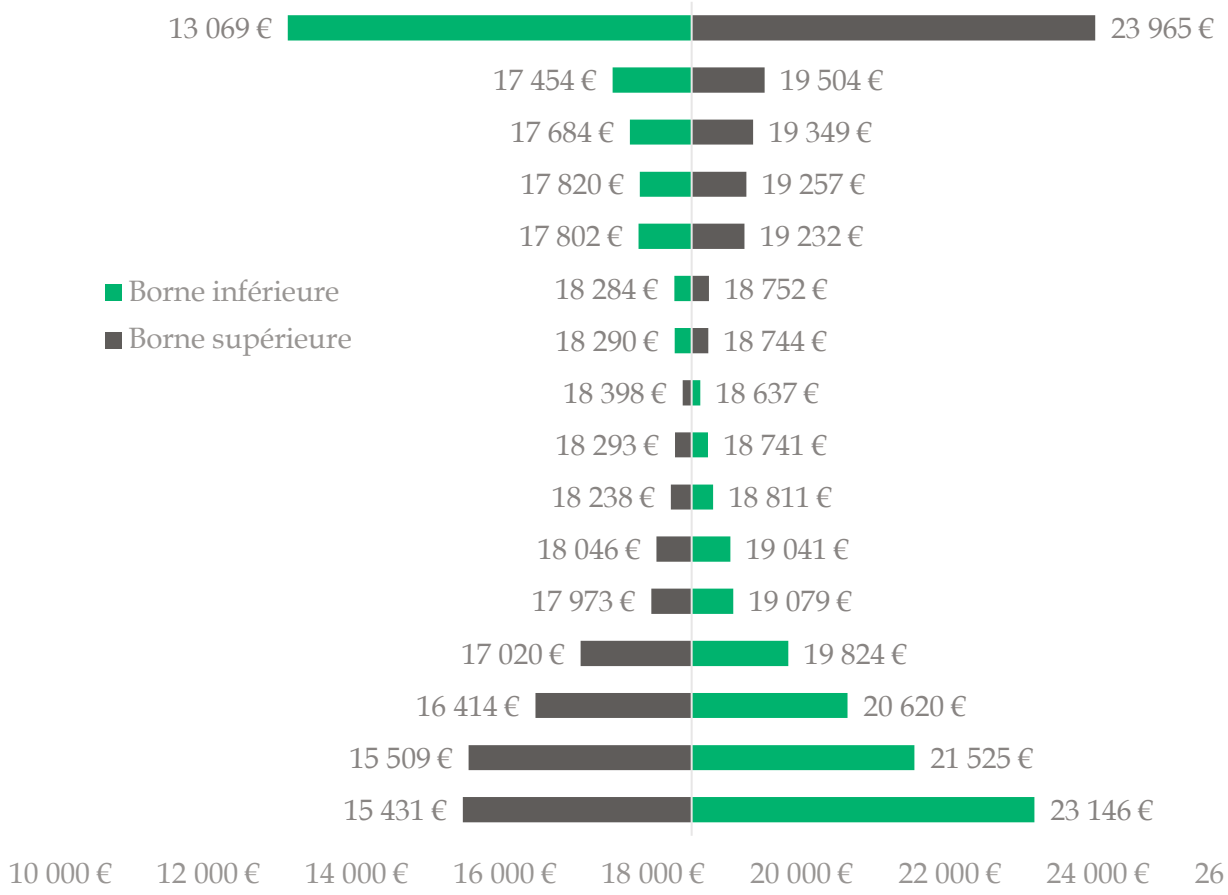
Teachings from the tornado chart



Mean dose of rifaximin

Sigma parameter of transition distribution from CHE2 to OHE2

Frequency of hospitalisations for rifaximin

- Tornado analysis displays the results of one-way sensitivity analyses for the variables in decreasing order of influence, and variations of each variable.
- The biggest ICER variation was obtained by
  - –changing the rifaximin-α mean dose,
  - –changing the transition probability CHE2 to OHE2,
  - –and frequency of hospitalizations.
- The other variable estimates do not have impact significantly the model when varied over a wide range

Frequency of hospitalisations for lactulose

Conversion factor CLDQEQ-5D

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Probabilistic sensibility analysis An example for a sample of 9 draws

- 1000 experiments - Storage of results in a numerical database

Calculation of Averages and differences of means

N° tirage	Lactulose		Rifaximine		Diff		ICER
	QALYs	Cost	QALYs	Cost	Δ QALYs	ΔCost	
1	1,27	6 925,44	1,94	13 929,52	0,67	7 004,07	10 445 €
2	2,49	11 161,39	3,15	20 884,48	0,66	9 723,09	14 833 €
3	2,89	9 992,23	3,41	23 998,71	0,52	14 006,48	26 812 €
4	0,81	4 730,33	1,56	11 180,91	0,75	6 450,58	8 608 €
5	1,65	6 773,71	2,24	15 138,95	0,59	8 365,24	14 134 €
6	2,16	8 605,70	2,82	18 339,09	0,66	9 733,39	14 704 €
7	1,26	6 502,00	1,85	13 954,19	0,59	7 452,19	12 643 €
8	1,14	4 441,84	1,72	11 717,84	0,58	7 276,00	12 577 €

- Each of the 9 draws represents one of the 1,000 trials run
- where each input was assigned a random value according to its probability density function.
- The average ICER over the all draws is equal to €13,507 (95% confidence interval [€8887–21,733]).

ΔICER = **13 507** €/Qalys **(IC 95% : [8 887€ - 21 733€])**

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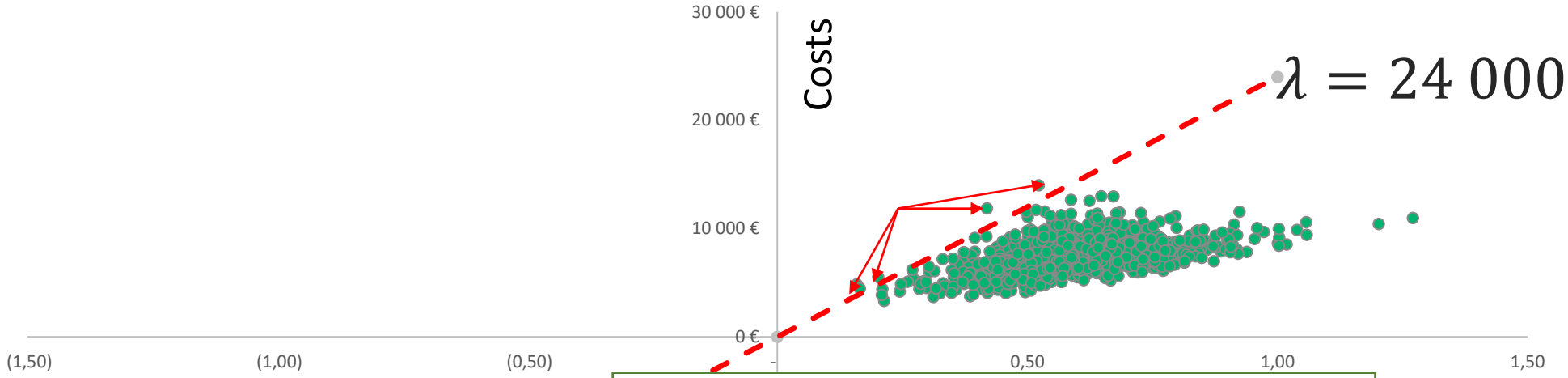
The scatter plot cost-effectiveness Plan
£ 24 000€ threshold



$N = 1\,000$ simulations

The horizontal axis displays the gain on additional quality-adjusted life years (QALYs) when using rifaximin-α instead of placebo,

The vertical axis displays the additional costs.

if a payer had a budget of €24,000 per QALY gained, then through all Monte Carlo simulations (broken line) only 4/ 1000 = 0.4% of the cohort would fall outside the budget.

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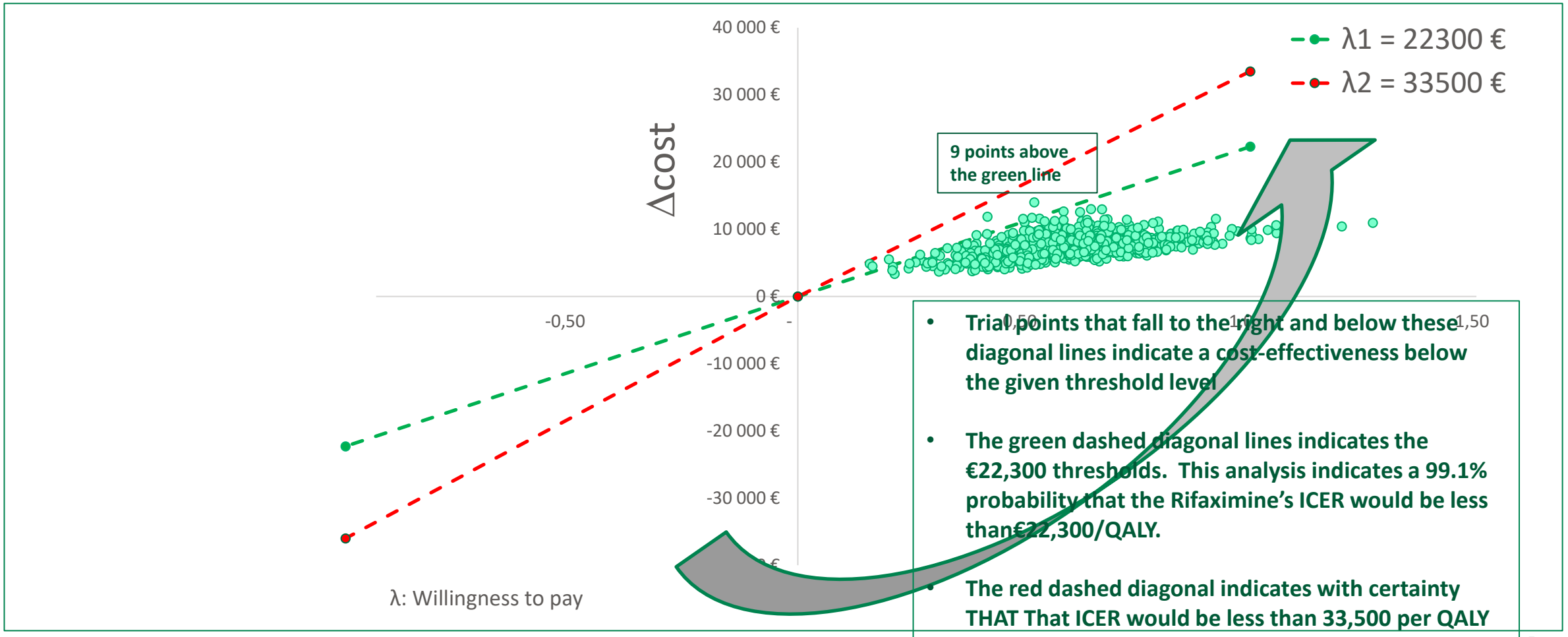
Outputs from the sensitivity analysis (€$_{09/2019}$)



- **Trial points that fall to the right and below these diagonal lines indicate a cost-effectiveness below the given threshold level**
- **The green dashed diagonal lines indicates the €22,300 thresholds. This analysis indicates a 99.1% probability that the Rifaximine's ICER would be less than€22,300/QALY.**
- **The red dashed diagonal indicates with certainty THAT That ICER would be less than 33,500 per QALY**

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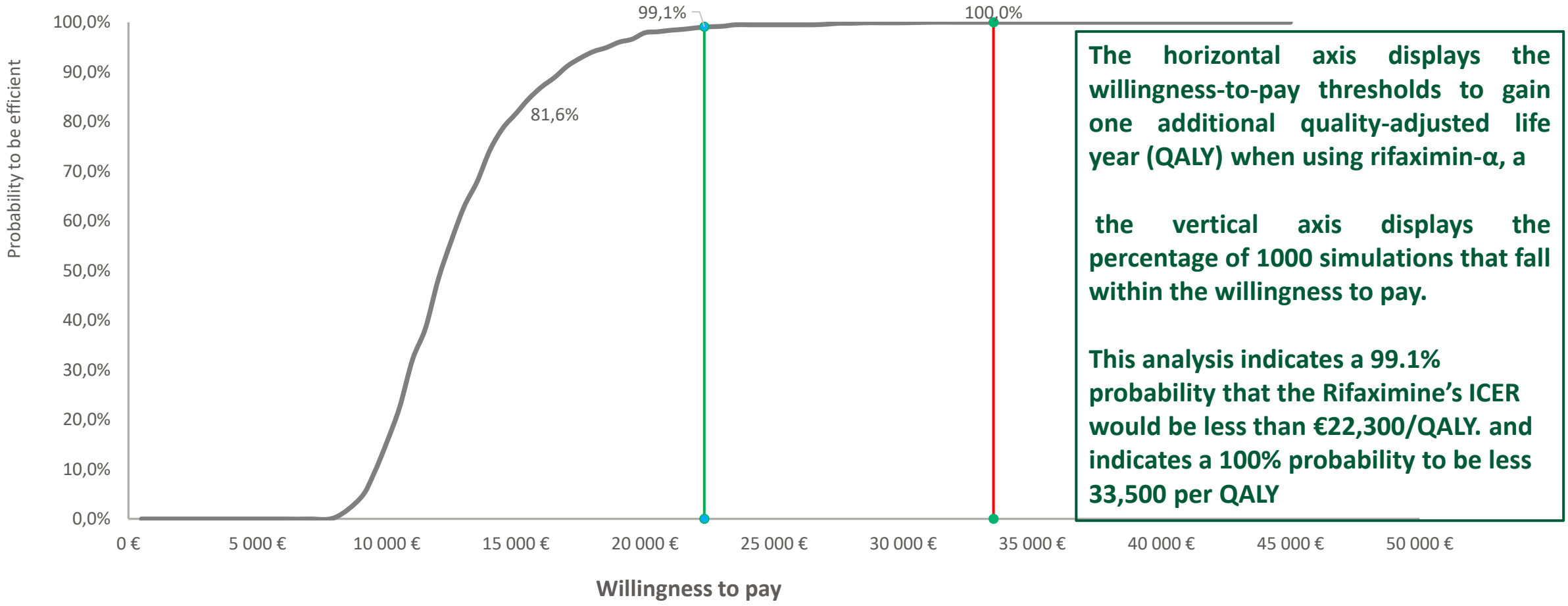
Cost effectiveness acceptability curve (CEAC)



The horizontal axis displays the willingness-to-pay thresholds to gain one additional quality-adjusted life year (QALY) when using rifaximin-α, a

the vertical axis displays the percentage of 1000 simulations that fall within the willingness to pay.

This analysis indicates a 99.1% probability that the Rifaximine's ICER would be less than €22,300/QALY. and indicates a 100% probability to be less 33,500 per QALY

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Conclusion

- The study reveals that in France for patients with recurrent HE in the context of liver cirrhosis rifaximin-α reduces episodes of overt HE.
- Rifaximin-α in association with lactulose improves the quality of life and reduces expenditure for the French healthcare system.
- rifaximin-α is a cost-effective treatment strategy when compared with lactulose monotherapy.
- The presented uncertainty intervals and cost-effectiveness acceptability curves enable decision-makers to appraise the results based on their risk aversion.

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THANK YOU FOR YOUR ATTENTION

Questions?

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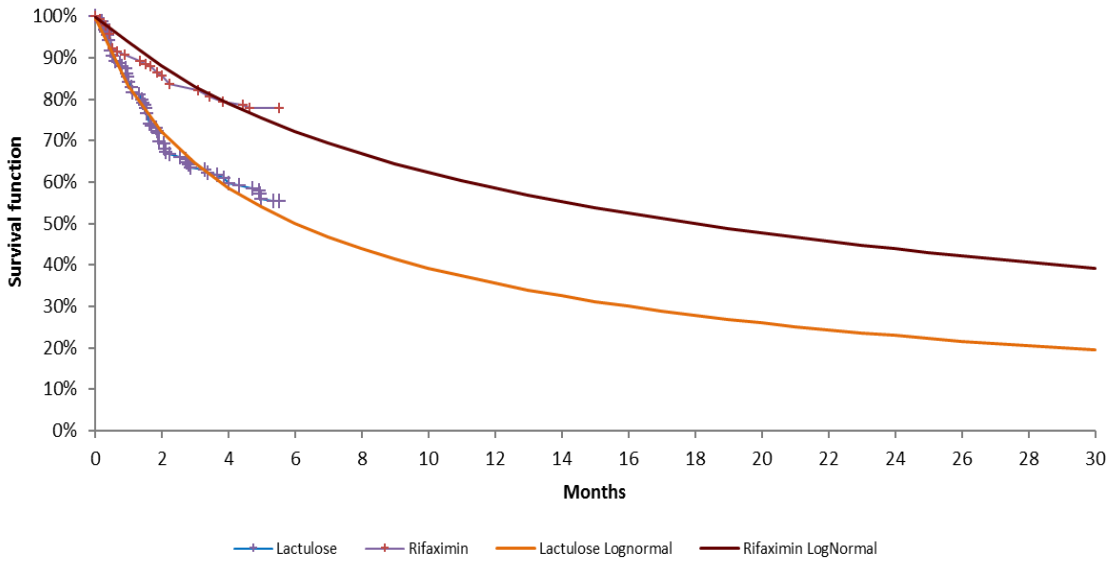
Example: estimating the time from CHE1 to OHE1

	Observations	Log likelihood	AIC	BIC
Exponential	299	-758,56	1519,11	1522,84
Weibull	299	-755,58	1513,16	1516,89
Gompertz	299	-749,02	1500,05	1503,78
Log-normale	**299**	**-748,68**	**1499,36**	**1503,09**
Log-logistic	299	-752,93	1507,87	1511,60



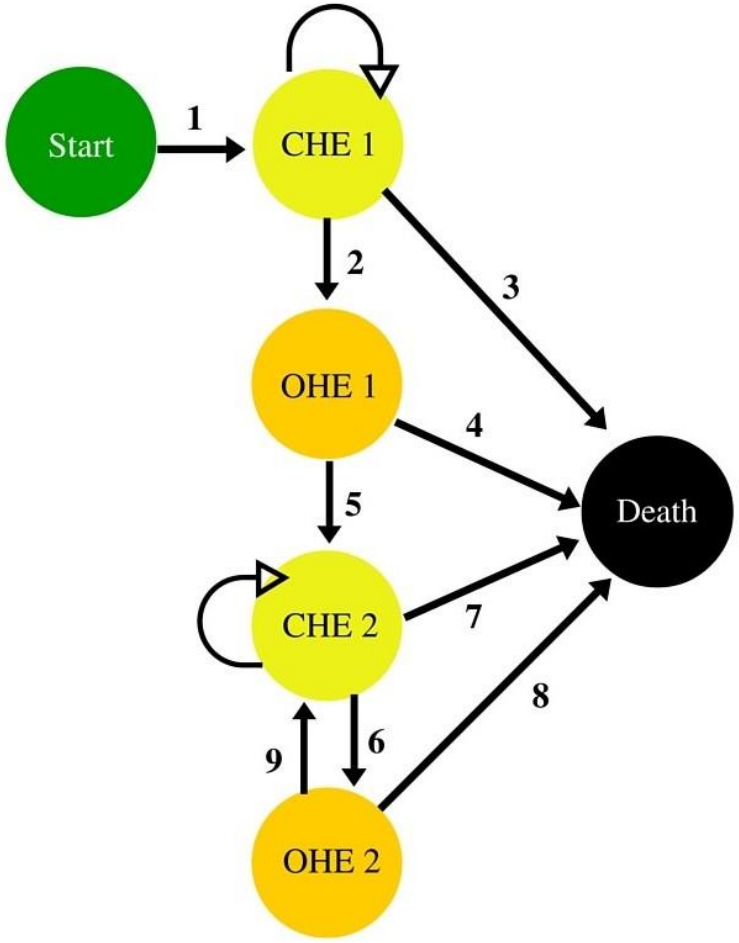
Graphical Comparison
Visual Inspection

Tests Statistiques

- Akaike Information Criterion(AIC)
- Bayesian Information Criterion (BIC)
- Log-vraisemblance (log(L))
- Log-cumulative hazard plot
- Résidus marginales

Clinical and External Validity
Assessment of clinical relevance of the extrapolated part of survival curve

Survival analysis for time-to-event data



Transitions	Parametric functions
2 : CHE1 -> OHE1	Log-normal parametric distribution. Discrete transition probabilities are calculated using Briggs (2006) formula
6 : CHE2 -> OHE2	α-Rifaximin arm: Log-normal parametric distribution. Lactulose arm : HR computed from RFHE3001
3 : CHE1 -> Death	Log-normal parametric survival distribution.
4 : OHE1 -> Death	RFHE3002 observed 30-days mortality(11,1%)
7 : CHE2 -> Death	Parametric survival distribution extrapolated from RFHE3002. From CHE until death or censor. Weibull distribution.
8 : OHE2 -> Death	OHE2 ->30 days observed mortality (7,7%)
5,9: Remission de OHE	Based on survival

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