SeHCAT (Tauroselcholic [^{75}Selenium] acid) for the investigation of bile acid diarrhoea: a systematic review and cost effectiveness analysis

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Addendum following the first Diagnostic Appraisal Committee meeting

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1. OUTSTANDING QUESTIONS

The objective of this document was to provide responses to the outstanding questions from the Diagnostics Advisory Committee (DAC) of [75Se] tauroselcholic acid (SeHCAT) for investigating bile acid diarrhoea (BAD). The meeting was held on 15 June 2021. There were two outstanding questions from the Committee:

- Why is the probability of response to bile acid sequestrants in the trial of treatment strategy assumed to be lower than the probability of response to bile acid sequestrants in the SeHCAT strategy? If the populations in these strategies were the same, wouldn't the response probability in the trial of treatment strategy to be expected to be the same or higher than in the SeHCAT strategy (because everyone who could respond gets treated and has the possibility to respond)? If the populations in these strategies are somehow different (the response probability is assumed higher in the SeHCAT strategy), wouldn't that mean that the model has problems with internal validity and is biased towards SeHCAT?
- Were the value sets used to calculate the utilities in Mearin et al. (2004)[1] and Spiegel et al. (2009)[2] from the UK? If not, were they somehow converted into UK applicable utilities?

Detail answers are provided in the following sections of this document.

2. EAG RESPONSE TO OUTSTANDING QUESTIONS

2.1 Probability of response to bile acid sequestrants

The probability of response to bile acid sequestrants in the trial of treatment strategy was estimated from experts' responses to our questionnaire. The probability of response to bile acid sequestrants in the SeHCAT 15% strategy was estimated from our systematic literature review.

The modelled populations in these strategies are the same. Patient characteristics are not included in the model as predictors of response to bile acid sequestrants or any other probability in the decision analytic model. There are two patient characteristics included in the model: age and gender proportion at baseline, which were sourced from the study by Summers et al. (2016),[3] we assumed that the average age in both populations was 50 years, and the ratio of male/female was 35/65. These characteristics are only used to calculate background mortality, which is applied in the Markov model but not in the decision analytic model.

In population 1, the estimated probability of a positive SeHCAT test at the 15% threshold was 0.454 (see Table 12 in the Diagnostic Assessment Report).[4] The estimated probability of response to bile acid sequestrants after a positive SeHCAT result was 0.638 (see Table 13 in the Diagnostic Assessment Report).[4] Thus, the estimated unconditional probability of response to bile acid sequestrants in the SeHCAT 15% strategy was 0.454*0.638 = 0.290. In the trial of treatment strategy, the probability of response to bile acid sequestrants was estimated using the responses from our questionnaire shown in Table 17 of the Diagnostic Assessment Report.[4] We estimated a mean of 0.300. Thus, in population 1, the probability of response to bile acid sequestrants in the trial of treatment strategy was slightly higher than in the SeHCAT strategy.

In population 2, the estimated probability of a positive SeHCAT test at the 15% threshold was 0.55 (see Table 27 in the Diagnostic Assessment Report).[4] The estimated probability of response to bile acid sequestrants after a positive SeHCAT result was 0.89 (see Table 28 in the Diagnostic Assessment Report).[4] Thus, the estimated unconditional probability of response to bile acid sequestrants in the SeHCAT 15% strategy was 0.55*0.89 = 0.490. In the trial of treatment strategy, the probability of response to bile acid sequestrants was estimated using the responses from our questionnaire shown in Table 32 of the Diagnostic Assessment Report.[4] We estimated a mean of 0.330. Thus, in population 2, the probability of response to bile acid sequestrants in the trial of treatment strategy was indeed lower than in the SeHCAT strategy. As mentioned in the Diagnostic Assessment Report,[4] the probabilities of a positive SeHCAT result and subsequent response to bile acid sequestrants were

estimated from Smith (2000).[5] Thus, these estimates were based on a small sample size and the relatively high response probability did not seem to be in line with experts' expectations, who in the answers to our questionnaire estimated this probability to be at most 0.7. Without a better estimate for the probability of a SeHCAT positive result, using the highest estimate given by the experts would result in an unconditional probability of response to bile acid sequestrants in the SeHCAT 15% strategy equal to 0.55*0.7 = 0.385, which is still higher than 0.330.

The EAG would like to emphasise that whether or not the response probability in the trial of treatment strategy is expected to be the same or higher than in the SeHCAT strategy is something that clinical experts will be better able to respond to than us. While it might seem reasonable to assume that in the trial of treatment strategy everyone who could respond to bile acid sequestrants would get the right treatment and, therefore, would have the possibility to respond; it might also be the case that patients will not respond for other reasons, e.g., patients with an undiagnosed or unclear condition might be less willing to take colestyramine, which could result in higher drop-out rates (and thus lower response) in the trial of treatment strategy. An additional point to consider is that clinical experts indicated that a response to bile acid sequestrants is not helpful diagnostically since these are constipating drugs in any event and it would be no better than using loperamide as a diagnostic test for any form of diarrhoea. Furthermore, patients treated with bile acid sequestrants are at risk of experiencing fat-soluble vitamin insufficiency and impaired absorption of other drugs. These "adverse events" are not included in the model due to lack of data but if it was possible to include them the (negative) impact would be larger in the trial of treatment strategy. Thus, some experts might consider that using bile acid sequestrants is not clinically justifiable without a definitive diagnosis in current practice.

In summary, to the best of our knowledge, the model has no problems with internal validity. If results are biased towards the SeHCAT 15% strategy, these are likely to be caused by the lack of (face) validity of input parameters like the probability of response to bile acid sequestrants. For this particular outstanding question, this seems to be problematic in population 2 only. This is not completely surprising given the lack of data for this specific population. Therefore, we would suggest to interpret the results for population 2 even with additional caution.

2.2 Utilities

Regarding utilities, we took the same approach as in the previous assessment of SeHCAT.[6] Thus, in population 1 there are two relevant studies: Spiegel et al. (2009)[2] and Mearin et al. (2004).[1] The first study is from the US and the second one from Spain. The utility values included in the model were directly sourced from these papers and were not converted into UK applicable utilities, thus, it was

implicitly assumed that these would be valid for the UK. The base-case utility values for population 1 are summarised in Table 1, where we have added UK transformed utilities using the algorithms in the eq5d R package.[7] Please be aware that only mean utility estimates were available for transformation, as patient level data was not available. Therefore, these transformed UK values represent crude estimates of a UK specific mean value. Differences in the utility values obtained from the different value sets are not consistent in size throughout the utility range, and tend to increase in size at the lower end of the utility scale. Given that patient level data is not available, this cannot be taken into account and therefore these transformed means may be subject to bias. Nevertheless, an additional scenario was run using the updated utilities. The results are presented in the next section.

Table 1: Base-case utility values for responders and non-responders, population 1

Non-responders/diarrhoea			
	Mean	Mean – UK transformed	SE
Mearin, 2004[1]	0.704	0.656	0.026
Spiegel, 2009 [2]	0.730	0.629	0.037
RE estimate	0.712	0.647	0.021
IBD/IBS-D/colesevelam responders/no diarrhoea			
	Mean	Mean – UK transformed	SE
Mearin, 2004[1]	0.775	0.719	0.014
Spiegel, 200 [2]	0.780	0.697	0.037
RE estimate	0.776	0.717	0.013
Colestyramine responders/no diarrhoea			
	Mean	Mean – UK transformed	SE
Assumption	0.760	0.700	0.020
Abbreviations: BAS = bile acid sequestrants, IBD = inflammatory bowel disease, IBS-D = diarrhoea predominant irritable bowel syndrome, RE = random effects, SE = standard error			

For population 2 we utilised the utility estimate from Buxton et al. (2007).[8] Since this is a UK study, the utilities for this population remain unchanged (see Table 33 in the Diagnostic Assessment Report).[4]

3. EAG ADDITIONAL SCENARIO ANALYSES

3.1 Alternative probability of SeHCAT positive result and response BAS treatment in population 1

We have not run additional scenarios on the probabilities of BAS response but we would like to highlight that the unconditional response to BAS treatment in the SeHCAT 15% strategy is obtained

by multiplying the probability of testing positive by the probability of response to BAS given tested positive. This probability has been added to Table 2 and Table 3 for clarity.

Table 2: Summary of SeHCAT positive and response to BAS scenarios, population 1

	SeHCAT 15% positive	Response to BAS | SeHCAT positive	Unconditional response to BAS in SeHCAT strategy	Response to BAS TOT
Base-case	0.454	0.638	0.290	0.299
Scenario 1	0.357	0.495	0.177	0.299
Scenario 2	0.555	0.760	0.422	0.299
Scenario 3	0.454	0.638	0.290	0.200
Scenario 4	0.454	0.638	0.290	0.400

Abbreviations: BAS = bile acid sequestrants, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

Table 3: Results of SeHCAT positive and response to BAS scenarios, population 1

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (response to BAS in SeHCAT strategy = 0.290, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2308	£2,236	£9,688
Scenario 1 (response to BAS in SeHCAT strategy = 0.177, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
SeHCAT 15%	60%	63%	£819	14.0031	£5,702	0.1789	£982	£5,489
BAS TOT	37%	65%	£507	14.0096	£7,449	0.0064	£1,747	£272,969
BAS scenario 2 (response to BAS in SeHCAT strategy = 0.422, BAS TOT response = 0.299)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	37%	65%	£507	14.0096	£7,449	Ext. dominated by SeHCAT 15%		
SeHCAT 15%	72%	74%	£748	14.1156	£8,423	0.2914	£3,703	£12,708
BAS scenario 3 (response to BAS in SeHCAT strategy = 0.290, BAS TOT response = 0.200)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			
BAS TOT	28%	61%	£566	13.9644	£6,857	Ext. dominated by SeHCAT 15%		
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2307	£2,236	£9,692
BAS scenario 4 (response to BAS in SeHCAT strategy = 0.290, BAS TOT response = 0.400)								
No SeHCAT	26%	47%	£557	13.8242	£4,720			

	Colo. avoided	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
SeHCAT 15%	65%	68%	£786	14.0550	£6,956	0.2307	£2,236	£9,692
BAS TOT	46%	70%	£446	14.0561	£8,059	0.0012	£1,103	£919,167

Abbreviations: BAS = bile acid sequestrants, Colo. = colonoscopy, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of colonoscopies avoided per patient. Percentage of response to any medication (thus, IBS-D, IBD or BAS). Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

3.2 Alternative health state utilities in population 1

We explored a scenario using the UK-transformed utilities shown in Table 1. Results are shown in Table 4. The lower utility values resulted in fewer QALYs gained for all strategies, as expected, but overall, results are in line with the base-case.

Table 4: Utility scenario results, population 1

	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case					
No SeHCAT	13.8242	£4,720			
BAS TOT	14.0096	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	14.0550	£6,956	0.2308	£2,236	£9,688
UK transformed utilities					
No SeHCAT	12.6648	£4,720			
BAS TOT	12.8711	£7,449	Dominated by SeHCAT 15%		
SeHCAT 15%	12.9208	£6,956	0.2560	£2,236	£8,733

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.

3.3 Alternative probability of SeHCAT positive result and response BAS treatment in population 2

As was done for population 1, we have not run additional scenarios on the probabilities of BAS response but we have highlighted the unconditional response to BAS treatment in the SeHCAT 15% strategy. This probability has been added to Table 5 and Table 6 for clarity. If there are concerns regarding the probability of response to BAS in the trial of treatment strategy, we refer to scenarios 1 and 5 below, which both describe a situation where the probability of response to BAS is higher in the trial of treatment strategy. In this scenario trial of treatment is dominant. However, as

mentioned below, we would like to emphasise that, given the lack of data, the results for this population should be interpreted with extra care.

Table 5: Summary of SeHCAT positive and response to BAS scenarios, population 2

	SeHCAT 15% positive	Response to BAS | SeHCAT positive	Unconditional response to BAS in SeHCAT strategy	Response to BAS TOT
Base-case	0.55	0.89	0.490	0.33
Scenario 1	0.39	0.67	0.261	0.33
Scenario 2	0.71	1.00	0.710	0.33
Scenario 3	0.55	0.89	0.490	0.23
Scenario 5	0.55	0.89	0.490	0.50
Abbreviations: BAS = bile acid sequestrants, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.				

Table 6: Results of SeHCAT positive and response to BAS scenarios, population 2

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
Base-case (response to BAS in SeHCAT strategy = 0.490, BAS TOT response = 0.339)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
SeHCAT 15%	71%	£1,061	13.0079	£14,131	0.1071	£185	£1,727
Scenario 1 (response to BAS in SeHCAT strategy = 0.261, BAS TOT response = 0.33)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
SeHCAT 15%	58%	£1,282	12.8700	£14,893	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946			
BAS scenario 2 (response to BAS in SeHCAT strategy = 0.710, BAS TOT response = 0.33)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	60%	£756	12.9008	£13,946	Dominated by SeHCAT 15%		
SeHCAT 15%	83%	£848	13.1411	£13,396			
BAS scenario 3 (response to BAS in SeHCAT strategy = 490, BAS TOT response = 0.23)							
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by BAS TOT		
BAS TOT	55%	£852	12.8399	£14,190	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131			
BAS scenario 4 (response to BAS in SeHCAT strategy = 0.490, BAS TOT response = 0.5)							

	Response	Initial costs	QALYs	Total costs	Inc. QALYs	Inc. Costs	ICER
No SeHCAT	40%	£1,052	12.6863	£14,419	Dominated by SeHCAT 15%		
SeHCAT 15%	71%	£1,061	13.0079	£14,131	Dominated by BAS TOT		
BAS TOT	70%	£586	13.0090	£13,511			

Abbreviations: BAS = bile acid sequestrants, ICER = incremental cost effectiveness ratio, Inc. = incremental, QALY = Quality-adjusted life year, TOT = trial of treatment, SeHCAT = Tauroselcholic [75Selenium] acid, TOT = trial of treatment.
Note: Percentage of response to any medication. Initial costs are those incurred in the first 6 months, i.e., those considered in the decision analytic model only.

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