Therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis [DAR17/10/02]

Addendum #4

15 April 2019

Commercial-in-confidence (CIC) information is marked as [redacted].

This Addendum was produced in response to a request from the National Institute for Health and Care Excellence (NICE) Technical Team for an exploratory analysis considering additional evidence (the INGEBIO full study report) submitted by the manufacturer of Promonitor test kits (Grifols), and comments received from the NICE Committee members and the company.

In Section 1, additional evidence from the INGEBIO full study report and the manuscript by Pascual-Salcedo et al. (2015) (see the reference below) are presented. In Section 2, additional analyses conducted by the External Assessment Group (EAG) are described:

- The cost-utility analysis carried out by Grifols was replicated using costs relevant to the NHS (Section 2.1).
- The original EAG's model was updated using
    - evidence from the INGEBIO full study report
    - amended costs of managing different health states

  (Section 2.2).

Summary of the outcomes

When the company's modelling approach (see INGEBIO full study report) was used, depending on the model assumptions the intervention was either dominant or cost-effective at the threshold of £20,000 per QALY gained (Table 4 and Table 5).

When the updated EAG's model was utilised, results varied considerably from the intervention being dominant to ICERs exceeding £160,000 per QALY gained (Table 9, Table 10, Table 11 and Table 12). Please, refer to the following sections for further details.

Dora Pascual-Salcedo, Plasencia Chamaida, Jurado Teresa, L González Del Valle, Sabina Prado, Diego Cristina, Villalba Alejandro, Bonilla Gema, Martín Mola Emilio and Balsa Alejandro J. Dose-tapering Of TNF inhibitors in daily rheumatology practice enables the maintenance of clinical efficacy while improving cost-effectiveness. Pharmacovigilance 2015, Vol 3(4): 172

1 Clinical effectiveness evidence

1.1 Additional data from the INGEBIO full report

Objective: To evaluate whether the difference in cumulative incidence of persistent disease flares with a duration of > 3 months between the group using Promonitor test and the standard care group does not exceed the non-inferiority margin of 20% after 18 months of treatment

Results: Relative risk = [redacted]

Table 1: Additional data on flares

	Outcome		
Groups	Persistent flare	No persistent flare	**Total**
Intervention	[redacted]	[redacted]	[redacted]
Control	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Conclusion:

[redacted]

1.2 Additional data from Pascual-Salcedo et al. (2015)

Objective: To assess whether the clinical activity remains stable after dose tapering of TNF inhibitors in patients with low disease activity.

Design: Observational study

The key differences between the paper by Pascual-Salcedo et al. (2015) and the abstract by Pascual-Salcedo et al. (2013):

- The 1st period reported in the paper by Pascual-Salcedo et al. (2015) was 2007-2009. However, the 1st period reported in the abstract by Pascual-Salcedo et al (2013) was 2006 - 2009.
- The paper by Pascual-Salcedo et al. (2015) reported that their analyses included those patients who received dose-tapering during the 2nd period. However, this was not clearly stated in the abstract by Pascual-Salcedo et al. (2013).

- The number of patients included in the paper by Pascual-Salcedo et al. (2015) was 77 patients (36 rheumatoid arthritis and 41 spondyloarthritis). However, the number of patients included in the abstract by Pascual-Salcedo et al. (2013) was 88 patients (43 rheumatoid arthritis and 45 spondyloarthritis).

Comparison: Standard care (1st Period) versus therapeutic drug monitoring (TDM) and dose-reduction (2nd Period)

Table 2: Additional Results

	1st Period (2007-2009)	**2nd Period (2010-2012)**	**p-value**
DAS28 (n=36 RA patients) (mean±SD)	2.28 ± 0.47	2.37 ± 0.50	0.20
Serum trough Drug level			
IFX (n=29) (mean±SD)	3.2 ± 2.5 µg/ml	1.8 ± 1.5 µg/ml	< 0.0001
ADA (n=27) (mean±SD)	5.5 ± 2.8 µg/ml	3.1 ± 2.1 µg/ml	<0.0001
ETN (n=21) (mean±SD)	1.8 ± 1.1 µg/ml	1.3 ± 0.8 µg/ml	<0.05
Interval of drug administration			
IFX (n=29) (mean±SD)	8.7 ± 1.4 weeks	9.85 ± 1.5 weeks	<0.001
ADA (n=27) (mean±SD)	2.3 ± 0.63 weeks	3.1 ± 1.02 weeks	<0.0001
ETN (n=21) (mean±SD)	1.4 ± 0.56 weeks	2.16 ± 1.57 weeks	<0.05

Key: IFX, infliximab; ADA, adalimumab; ETN, etanercept; DAS, disease activity score; RA, rheumatoid arthritis

2 Additional analyses conducted by the EAG

2.1 Cost-utility analysis from the INGEBIO full study report, adapted to the UK setting

2.1.1 Assumptions

2.1.1.1 Costs

The additional analysis based on the INGEBIO full study report included the same cost components as the company's analysis. Those were:

- Drug acquisition costs
- The costs of hospital admissions and visits to specialists
- The cost of therapeutic drug monitoring (TDM) and other (non-TDM) testing

Of note, the company did not take into consideration the cost of RA surgery; however, based on the clinical evidence from the INGEBIO study report, these costs were similar in the intervention and control arms, and therefore were not included in the additional analysis conducted by the EAG.

We derived the differential drug acquisition cost in GBP (estimated as *the cost of treatment in the intervention arm – cost in the control arm*) using the formula:

$$\textbf{differential cost in EURO} / \textbf{cost per vial in EURO} * \textbf{cost per vial in GBP}$$

The mean differential cost of treatment was [redacted] per person per 18 month follow-up period (p. 48, INGEBIO report). The company wrote however that the difference was significantly lower in *patients with rheumatoid arthritis*: it was [redacted] per person per 18 month follow-up. We examined the effect of this on the cost-effectiveness outcomes in sensitivity analyses (see Table 5).

The cost of adalimumab 40 mg/ml vial in the company's analysis was [redacted] (p. 48, INGEBIO report); the respective cost in GBP obtained from BNF was £352.14 per vial (as in the EAG's original report).

The costs of hospital admissions and visits to specialists, and the costs of other (non-TDM) tests were estimated from the frequency of resource use in the INGEBIO study and the NHS Reference Costs (Table 3).

Table 3: Unit costs and the frequency of resource use per 18 months (as in INGEBIO)

Resource	*Unit cost*[1]	*Frequency of resource use*[2]

		Intervention	Control
Inpatient day (HD23J)	£413	[redacted]	[redacted]
Outpatient attendance rheumatology	£146	[redacted]	[redacted]

[1] NHS Reference Costs[1] (assumed in the EAG's primary analysis)
[2] Source: Table on p. 46 (INGEBIO full study report)

The cost of non-TDM testing was [redacted], with the differential cost of [redacted] per 18 months (p. 46, INGEBIO full study report).

The costs of visits to Intensive Care Unit (ICU) were [redacted].

The other assumptions in the EAG's analysis were as follows:

- The frequency of drug-level testing of [redacted] per patient per year (based on the mean number of [redacted] tests per follow-up period of 18 months, p.49, INGEBIO report)
- The costs of the test kits provided by the manufacturer (as in our original report)
- The other costs of TDM testing as in Jani et al. (2017)[2] (refer to our original report)
- Reflexive testing of drug and antibody levels (singlet dilution) in a UK laboratory assuming that [redacted] of patients require antibody testing (as in the INGEBIO report)
- An *initial* phlebotomy appointment (for collection of a blood sample for drug-level testing) as in Jani et al. (2017)[2]
- Zero administration cost for adalimumab
- No treatment wastage

2.1.1.2 QALYs

As stated in the INGEBIO full study report, [redacted] (refer to p. 44 and graph on p. 46 of the INGEBIO full study report). At the end of the 18 month follow-up period, utility estimates differed [redacted] ([redacted] and [redacted] in the intervention and control arms, respectively).

The QALY differential over 18-month follow-up period, estimated in the company's analysis, was [redacted] (Table 4).

Given that (1) the intervention group had a [redacted] when compared to the control group, (2) patients from both arms had [redacted], and

(3) this study had a relatively small patient population - [redacted] and [redacted] patients in the intervention and control arms, respectively (which might explain, at least partially, the irregular variation of the utility values over the follow-up period as shown on p. 46 of the company's report) - the EAG believes that the actual QALY differential is likely to be lower than the company's estimate.

The QALY differential, estimated by Grifols using Spanish utility tariff, was assumed in the EAG's additional analysis, which is a limitation of this analysis.

2.1.2 Results

The outcomes of the base-case analysis are given in Table 4.

Table 4: Base-case results for the overall patient population in the INGEBIO study

	Intervention arm	Control arm	Intervention vs. control
QALYs (per 18 months)[1]	[redacted]	[redacted]	[redacted]
Acquisition costs			[redacted]
Other costs	£1,643	*£906*	£737
Total costs (per 18 months)			**-£386**
ICER (Cost / QALY gained)			*ICER not relevant - Intervention dominates standard care*

[1] INGEBIO full study report (p. 55)

The mean differential cost over 18 month period was -£386 (which corresponds to *-£257 per year*), and therefore the intervention dominated standard care.

When the *differential cost of drug acquisition* estimated by the company for the *RA patient subpopulation* ([redacted] per person per 18 month follow-up, see Section 2.1.1.1) was assumed, the mean differential cost per 18 months was £419 *(£280 per year*), with the ICER of about £5,000 per QALY gained.

The outcomes of sensitivity analyses are given in Table 5.

Table 5: Sensitivity analyses

Sensitivity analysis		Overall patient population		Subpopulation of RA patients[1]	
		Differential cost (£ per patient per year)	*ICER*	*Differential cost (£ per patient per year)*	*ICER*
Frequency of testing (#tests per year):	1	-£624	Intervention dominates SC (in all scenarios below)	-£87	Intervention dominates SC
	2	-£491		£46	£800
Duplicate concurrent testing with phlebotomy appointment		-£159		£378	£6,629
Duplicate reflex testing with phlebotomy appointment, 35.8% of patients w/LDL		-£199		£337	£5,919
Duplicate reflex testing with phlebotomy appointment, [redacted] of patients w/LDL		-£225		£316	£5,542
Singlet reflex testing with phlebotomy appointment, 35.8% of patients w/LDL		-£244		£293	£5,140
Singlet reflex testing with phlebotomy appointment, [redacted] of patients w/LDL		-£257		£280	£4,904
Singlet reflex testing without phlebotomy appointment, [redacted] of patients w LDL		-£663		-£126	Intervention dominates SC (in all scenarios below)
Singlet reflex testing without phlebotomy appointment, 35.8% of patients w/LDL		-£649		-£112	
Duplicate reflex testing without phlebotomy appointment, [redacted] of patients w/LDL		-£626		-£90	
Singlet concurrent testing without phlebotomy appointment		-£630		-£93	
Duplicate reflex testing without phlebotomy appointment, 35.8% of patients w/LDL		-£605		-£68	
Duplicate concurrent testing without phlebotomy appointment		-£564		-£28	

Key: LDL, low drug level; N/A, not applicable (intervention dominates standard care); SC, standard care

[1] In these analyses, only the drug acquisition costs are specific to the RA patient subpopulation, with all the other parameters assumed to be the same as for the overall patient population.

2.2 Amended EAG's model

2.2.1 Assumptions

In response to comments from the NICE Committee members and in light of the new evidence provided by the company (see Section 1), we now propose an additional analysis which uses (1) lower costs of managing health states, and (2) the estimates on persistent disease flares with a duration of > 3 months for the intervention and control arms, duration of remission, the mean time to first flare, flare rate and the number of tests used in the company's analysis. These amendments are detailed in

Table 6, along with other model assumptions, **in bold**.

Table 6: Comparison of assumptions in the company's and EAG's analyses

Assumption	INGEBIO full study report		EAG's primary analysis			
			Ucar 2017		*Arango 2017*	
	Intervention (N=97)	Control (N=52)	Intervention (N=109)	Control (N=60)	Intervention (N=98)	Control (N=52)
Duration of follow-up	530.8	544.6	499	505	530.8	544.6
Duration of remission (days)	362.2	360	344	329	N/A	N/A
Time to first flare (days)	[redacted]	[redacted]	208.07	189.32	208.07	189.32
The rate of flares per patient/year	[redacted]	[redacted]	0.463	0.639	0.463	0.639
Number of tests (per year)	[redacted]	N/A	1	1	1	1
Utilities	Estimated from EQ-5D-5L data using the Spanish tariff		**Estimated by mapping HAQ scores to EQ-5D-3L using UK tariff**			
Initial phlebotomy appointment	Not costed		**Costed (as in Jani et al (2017)[2])**			
Singlet or duplicate	Not stated but likely singlet (given test kit price)		**Singlet**			
Concurrent or reflex	**Reflex assuming [redacted] of ptxs w/LDL**		Concurrent			
Wastage	Not modelled		**£370 per person per year**			
Flare type	Persistent flares (see **Error! Reference source not found.**		**Type A flares (Table 7)**			

Key: ADL, adalimumab; LDL, low drug level; NR, not reported
Note: Assumptions in the

Assumption	INGEBIO full study report		EAG's primary analysis			
			Ucar 2017		*Arango 2017*	
	Intervention (N=97)	Control (N=52)	Intervention (N=109)	Control (N=60)	Intervention (N=98)	Control (N=52)
	updated EAG's analysis are shown **in bold**. [1] The mean duration of flares assumed in the additional EAG's analyses was 3 months (90 days).)					
Flare duration	**3 months[1]**		7 days			
	or more					
Tapering dose	NR		**2/3 of the full dose**			
% of flared ptxs in whom full ADL dose is restored	NR		**100%**			

Key: ADL, adalimumab; LDL, low drug level; NR, not reported

Note: Assumptions in the updated EAG's analysis are shown **in bold**.

[1] The mean duration of flares assumed in the additional EAG's analyses was 3 months (90 days).

Table 7: Definition of flares in the company's and EAG's analyses

Type of flare	DAS28		
	current	previous	increase
EAG's analyses			
A (base case)	>2.4	any	≥0.6
Minor B (sensitivity analysis)	>2.4	≤2.4	<0.6
Major B [1] (sensitivity analysis)	>2.4	≤2.4	≥0.6
Company's analysis			
Persistent flare			>1.2
or			
	≥3.2		>0.6

Key: DAS28, disease activity score in 28 joints

[1] Major B is a subcase of A.

The amended costs of managing health states are shown in Table 8.

Table 8: Costs of managing different health states

Health state	Cost (£ per patient per year)
Remission	£902
LDA/active disease	£1,483
Remission/LDA	£1,089

Health state	Cost (£ per patient per year)
Active disease	£1,827

Key: LDA, low disease activity

These costs are substantially lower than the estimates used in the original report.

2.2.2 Results of the cost-utility analysis

Results of the updated cost-utility analysis (using the EAG's original model) are shown in Table 9.

Table 9: Updated EAG's primary cost-utility analysis based on the INGEBIO report

	Intervention arm	Control arm	Intervention vs. control
Scenario 1 with mean duration of remission: intervention – *362.2* days, control – *360* days[1]			
Total costs (mean)	£16,170	£15,714	£457
QALYs (mean)	0.972	0.963	0.009
ICER (Cost / QALY gained)			£51,929
Scenario 2 with mean duration of remission/LDA: intervention – [redacted] days, control – [redacted] days[1]			
Total costs (mean)	£16,316	£15,839	£477
QALYs (mean)	0.929	0.926	0.004
ICER (Cost / QALY gained)			£125,272

Key: ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year
[1] INGEBIO full report (p. 41)

Cost-effectiveness results under different discounts for adalimumab (Humira®) are given in Table 10.

Table 10: Cost-effectiveness of TDM under different discounts for adalimumab (Humira®)

Discount	Intervention arm	Control arm	Cost differential	QALY differential	ICER
Scenario 1 with mean duration of remission: intervention – *362.2* days, control – *360* days[1]					
20% ADA discount	£13,510	£13,024	£486	0.009	£55,249
40% ADA discount	£10,850	£10,334	£515		£58,568
60% ADA discount	£8,189	£7,645	£544		£61,888
80% ADA discount	£5,529	£4,955	£574		£65,207

Discount	Intervention arm	Control arm	Cost differential	QALY differential	ICER
Scenario 2 with mean duration of remission/LDA: intervention – [redacted] days, control – [redacted] days[1]					
20% ADA discount	£13,655	£13,149	£506	0.004	£132,942
40% ADA discount	£10,995	£10,460	£535		£140,613
60% ADA discount	£8,335	£7,770	£564		£148,283
80% ADA discount	£5,674	£5,080	£594		£155,954

[1] INGEBIO full report (p. 41)

Results of other sensitivity analyses are presented in Table 11 and Table 12.

Table 11: Sensitivity analyses for Scenario 1 (with mean duration of remission[1])

Sensitivity analysis	Assumptions	Results			Source
		Cost differential	*QALY differential*	*ICER*	
Impact of flares only (health states and AEs are not included)	Only flares contribute to differential costs and QALYs	£461	0.008	£58,452	Scenario C (Gavan 2017[3])
Tapering strategy	Spacing: ADL dose to 40mg every 4 weeks	£384	0.009 (in all scenarios below)	£43,631	EAG's report, Appendix 5
Treatment wastage	No wastage	£462		£52,572	Clinical advice
Proportion of flared patients in whom full dose is restored	55%	£499		£56,760	Bykerk et al. (2014)[4] and clinical advice
	0%	£551		£62,665	
Frequency of testing (tests/year)	1	-£94		Intervention dominates SC	Clinical advice (in all scenarios below)
	2	£106		£12,035	
Duplicate concurrent testing with phlebotomy appointment		£604		£68,693	
Duplicate reflex testing with phlebotomy appointment, 35.8% of patients w/LDL[3]		£544		£61,795	
Singlet reflex testing with phlebotomy appointment, 35.8% of patients w/LDL[3]		£477		£54,220	

Sensitivity analysis	Assumptions	Results			Source
		Cost differential	*QALY differential*	*ICER*	
Singlet reflex testing without phlebotomy appointment, [2] [redacted] of patients w LDL		-£151		Intervention dominates SC (in all scenarios below)	
Singlet reflex testing without phlebotomy appointment, [2] 35.8% of patients w/LDL[3]		-£131			
Duplicate reflex testing without phlebotomy appointment, [2] [redacted] of patients w/LDL		-£97			
Singlet concurrent testing without phlebotomy appointment[2]		-£102			
Duplicate reflex testing without phlebotomy appointment, [2] 35.8% of patients w/LDL[3]		-£65			
Duplicate concurrent testing without phlebotomy appointment[2]		-£4			

[1] The mean duration of remission is 362.2 and 360 days in the intervention and control arms, respectively (INGEBIO full study report, p. 41).

[2] The cost of testing does not include the cost of an additional phlebotomy appointment which might not be required if people will receive regular hematological analysis as part of on-going treatment.

[3] About 35.8% of people with RA have low drug level (Laine and colleagues 2016). This estimate was used in the original EAG's analysis as an upper bound for reflex testing.

Key: ICER, incremental cost-effectiveness ratio; LDL, low drug level; SC, standard care

Notes: All costs are reported in 2017-18 prices.

Table 12: Sensitivity analyses for Scenario 2 (with mean duration of remission/LDA[1])

Sensitivity analysis	Assumptions	Results			Source
		Cost differential	*QALY differential*	*ICER*	
Tapering strategy	Spacing: ADL dose to 40mg every 4 weeks	£404	0.004 (in all scenarios below)	£106,095	EAG's report, Appendix 5
Treatment wastage	No wastage	£482		£126,756	Clinical advice
Proportion of flared patients in whom full dose is restored	55%	£519		£136,466	Bykerk et al. (2014) [4] and clinical advice
	0%	£571		£150,161	
Frequency of testing (tests/year)	1	-£73		Intervention dominates SC	Clinical advice (in all scenarios below)
	2	£126		£33,082	

Sensitivity analysis	Assumptions	Results			Source
		Cost differential	*QALY differential*	*ICER*	
Duplicate concurrent testing with phlebotomy appointment		£624		£164,009	
Duplicate reflex testing with phlebotomy appointment, 35.8% of patients w/LDL[3]		£564		£148,070	
Singlet reflex testing with phlebotomy appointment, 35.8% of patients w/LDL[3]		£497		£130,564	
Singlet reflex testing without phlebotomy appointment, [2] [redacted] *of patients w LDL*		-£131		Intervention dominates SC	
Singlet reflex testing without phlebotomy appointment, [2] *35.8% of patients w/LDL*[3]		-£111			
Duplicate reflex testing without phlebotomy appointment, [2] [redacted] *of patients w/LDL*		-£77			
Singlet concurrent testing without phlebotomy appointment[2]		-£82			
Duplicate reflex testing without phlebotomy appointment, [2] *35.8% of patients w/LDL*[3]		-£45			
Duplicate concurrent testing without phlebotomy appointment[2]		£16		£4,230	

[1] The mean duration of remission/LDA is [redacted] and [redacted] days in the intervention and control arms, respectively (INGEBIO full study report, p. 41).

[2] The cost of testing does not include the cost of an additional phlebotomy appointment which might not be required if people will receive regular hematological analysis as part of on-going treatment.

[3] About 35.8% of people with RA have low drug level (Laine and colleagues 2016). This estimate was used in the original EAG's analysis as an upper bound for reflex testing.

Key: ICER, incremental cost-effectiveness ratio; LDA, low disease activity; LDL, low drug level; SC, standard care

Notes: All costs are reported in 2017-18 prices.

1. NHS. Reference costs 2017 [Available from: https://improvement.nhs.uk/resources/reference-costs/.

2. Jani M, Gavan S, Chinoy H, Dixon WG, Harrison B, Moran A, et al. A microcosting study of immunogenicity and tumour necrosis factor alpha inhibitor drug level tests for therapeutic drug monitoring in clinical practice. Rheumatology (Oxford). 2016;55(12):2131-7.

3. Gavan S. An economic evaluation of a biomarker test to stratify treatment for rheumatoid arthritis: The University of Manchester; 2017.

4. Bykerk VP, Shadick N, Frits M, Bingham CO, Jeffery I, Iannaccone C. Flares in rheumatoid arthritis: frequency and management. A report from the BRASS registry. J Rheumatol. 2014;41.