Theradiag

LISA TRACKER Duo Adalimumab

REF **LTA 005**

2 x 48

42 determinations

English

DEFINITION

LISA-TRACKER Duo Adalimumab (Theradiag) is an enzyme linked immunoassay (ELISA) for the quantitative determination of Adalimumab (anti-TNFα) and anti-Adalimumab antibodies in human serum samples. These tests can be separatly or simultaneously done by following the standardized assay protocole.

DIAGNOSTIC VALUE

Anti-TNFα are therapeutic agents widely used to treat patients with various inflammatory diseases. Adalimumab is one of the anti-TNFα recommended for the treatment of the rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, etc. This fully humanized monoclonal antibody is able to bind TNFα. It blocks the action of TNFα responsible for the inflammatory state. However, during the treatment, some patients can develop antibodies against Adalimumab. Consequently, the plasmatic level of anti-TNFα decreases and simultaneous the disease symptoms reappear or increase.

LISA-TRACKER Duo Adalimumab (Theradiag) allows the detection of 2 parameters: Adalimumab and anti-Adalimumab antibodies. This kit allows the physician to monitor the level rate of these 2 parameters in patient sera.

SAMPLES COLLECTION AND HANDLING

- The test should be performed on plasma (EDTA, heparin or citrate collection tubes) or on serum.
- Samples which have been frozen and defrosted more than once, should be avoided.
- To avoid any non-specific binding, samples which have been frozen for more than 6 months or which are cloudy, should be centrifuged and filtered.

ASSAY PRINCIPLE

LISA-TRACKER Duo Adalimumab (Theradiag) is validated to monitor drug levels and anti-drug antibody levels of any biological drug which contains the active substance Adalimumab, that is the original drug Humira®, and any biosimilar drug like SB5 (Imraldi®).

A. Dosage of Adalimumab

The TNFα is coated onto a polystyrene microtiter plate (6 strips of 8 wells).

- First, the diluted sample is added to the TNFα coated well, which allows to bind. After incubation, unbound proteins are removed by washing.
- Biotinylated polyclonal rabbit anti-Adalimumab antibody is added. After incubation, unbound antibodies are removed by washing
- Then horseradish peroxydase labelled streptavidin is added. The streptavidin binds to the complex formed with biotinylated anti-ADA antibodies. After incubation, the wells are washed again to eliminate any excess of conjugate.
- The bound enzyme is revealed by addition of substrate TMB (3,3',5,5' tetramethylbenzidin). The colour intensity is proportional to the amount of Adalimumab.
- Adding H_2SO_4 allows to stop the enzymatic reaction.
- After stopping the reaction by H_2SO_4, the optical density is read by a spectrophotometer at 450nm.

A range of calibration allows to define the quantity of Adalimumab of each patient samples expressed in µg/mL.

B. Dosage of anti-Adalimumab

The Adalimumab is coated onto a polystyrene microtiter plate (6 strips of 8 wells).

- First, the diluted sample is added to the antibody coated well, which allows to bind. After incubation, unbound proteins are removed by washing.
- Biotinylated Adalimumab is added. After incubation, unbound antibodies are removed by washing.
- Then horseradish peroxydase labelled streptavidin is added. The streptavidin binds to the complex formed with biotinylated Adalimumab. After incubation, the wells are washed again to eliminate any excess of conjugate.
- The bound enzyme is revealed by addition of substrate TMB (3,3',5,5' tetramethylbenzidin). The colour intensity is proportional to the amount of anti-Adalimumab antibodies.
- Adding H_2SO_4 allows to stop the enzymatic reaction.
- After stopping the reaction by H_2SO_4, the optical density is read by a spectrophotometer at 450nm.

A range of calibration allows to define the quantity of anti-Adalimumab antibodies of each patient samples expressed in ng/mL.

REAGENTS

3 reagent families :

Color	Adalimumab reagents	anti-Adalimumab antibodies reagents	Common reagents
cap of vials	**Blue**	**Brown or Black**	**Green, White, Black or Purple**
microwells	**Blue**	**Black**	**-**

A) Specific reagents for the Adalimumab determination

Strips of individual breakaway blue wells coated with human TNFα MP	6 strips
5 vials of « Adalimumab » Standards, (µg/mL). Ready to use. ADA CAL n The vials can be reused several times. ***The quantity of Adalimumab is indicated on the vial label*** ***Blue caps***	5 x 1.5mL
«Positive control - Adalimumab», (µg/mL). To dilute. ADA CONTROL + The vials can be reused several times. ***The quantity of Adalimumab is indicated on the vial label*** ***Blue cap***	1 x 250µL
Biotinylated antibody vial. Ready to use ADA Ab BIOT ***Blue cap***	1 x 7.5mL

B) Specific reagents for the anti-Adalimumab antibodies determination

Strips of individual breakaway black wells coated with Adalimumab. MP	6 strips
5 vials of « anti-Adalimumab » Standards, (ng/mL). A-ADA CAL n Ready to use. The vials can bed reused several times. ***The quantity of anti-Adalimumab is indicated on the vial label*** ***Brown cap.***	5 x 1.5mL
« Positive control – anti-Adalimumab», (ng/mL). To dilute. A-ADA CONTROL + The vial can be reused several times. ***The quantity of anti-Adalimumab is indicated on the vial label.*** ***Brown cap***	1 x 1mL
Biotinylated antibody vial. Ready to use. A-ADA Ab BIOT ***Black cap.***	1 x 7.5mL

C) Common reagents

HRP labelled Streptavidin. Ready to use. CONJ HRP ***Green cap.***	1 x 12mL
Phosphate-Tween Buffer pH 7,2 (10x) – To reconstitute with distilled water. ***White cap.*** BUF WASH 10x	1 x 100mL
Substrate (TMB). Ready to use SUBS TMB ***Black cap.***	1 x 12mL
Stop solution - H_2SO_4 (0.25 N). Ready to use. SOLN STOP ***Purple cap***	1 x 15mL

MATERIAL REQUIRED BUT NOT PROVIDED

- distilled water
- precision pipettes
- microplate spectrophotometer with 450 nm filter
- 8 channel pipettes

STABILITY AND STORAGE

- Store reagents and micro-wells at +2°C/+8°C in their own package.
- Do not use kits beyond the expiration date.
- Store unused strips into their plastic bag (closed securely) with the desiccant.
- Store all components immediately after use again at +2°C/+8°C.

SETUP

Except the TDL, which can be prepare in advance, all reagents must be prepared extemporaneously.

1. Dilution and Wash buffer (TDL)

- Dilute concentrated Phosphate-Tween Buffer 1/10 in distilled water.

BUF WASH 10x

- Shelf life : 3 months at +2°C/+8°C (avoid to use if signs of contamination or other visible changes occur).

NB. If there are crystals in the concentrated solution, warm the bottle up to +37°C for 15 minutes before use.

2. Preparation of samples and positive controls

a. Samples
- Adalimumab determination

- Dilute to 1/201 in TDL

Ex : 5µL sample + 1mL TDL
Vortex vigorously.

- Anti-Adalimumab determination

- Dilute to 1/2 in TDL

Ex : 130µL sample + 130µL TDL
- Vortex vigorously.

b. Positive controls
- Adalimumab determination

- Dilute to 1/201 in TDL

Ex : 5µL positive control + 1mL TDL
- Vortex vigorously.

- Anti-Adalimumab determination

- Dilute to 1/2 in TDL

Ex : 130µL positive control + 130µL TDL
- Vortex vigorously.

3. Use of ready-to-use biotinylated antibody.

- Estimate the amount required for handling and transfer to a tube.

4. Use of ready-to-use HRP Streptavidin conjugate.

- Estimate the amount required for handling and transfer to a tube.

5. Use of ready-to-use substrate.

- Estimate the amount required for handling and transfer to a dark tube.

PRECAUTIONS

Unpack all reagents in order to let them warm at room temperature (+18°C/+25°C) at least half an hour before starting the test.

☝ The temperature of the reagents can impact the final result.

Check that all plates are well drained after each wash.

Avoid to use reagents if signs of contamination or other visible changes occur.

Human sources for the preparation of standards and controls have been tested and found negative for antibody to HIV 1 and 2, antibody to hepatitis C virus and hepatitis B virus antigen. Nevertheless, no test can offer complete assurance that HIV, hepatitis B virus or other infectious agents are absent. Therefore, the reagents should be handled as potentially infective materials.

Reagents in solution (except for substrate buffer and stop solution) contain <0.1% of sodium azide and <0.6% of ProClin® 300. Do not eat and avoid contact with skin and eyes. Azide can form explosive mixtures in copper or lead piping. Rinse thoroughly after flushing.

-  At this concentration, ProClin® 300 is irritating to eyes and skin, and may be detrimental if enough quantity is ingested. It is a skin sensitizer; prolonged or repeated exposure may cause allergic reaction in certain sensitive individuals.

LISA-TRACKER Duo Adalimumab (Theradiag) has been developed according to EC regulation n°1272/2008 relating to the classification, labelling and packaging of substances and mixtures.

LISA-TRACKER Duo Adalimumab (Theradiag) has been optimized for the use as describe in this procedure. Do not substitute other manufacturer's reagents. Dilution or adulteration of these reagents may also affect the performance of the test. Close adherence to the test procedure will assure optimal performance.

METHOD

1. Preparing the test

Use the work sheet to note the sample locations.

Set out (for each specificity):

- 5 "standard" wells
- 1 well for positive control
- 1 well for each sample

For a simultaneous testing of the 2 parameters, detach the exact number of wells needed. Return unused wells to plastic pouch provided in the kit, with the desiccant bag.

Remark :

If a dispensing/diluting device is used, place the specific wells in the following order : dosage of Adalimumab then dosage of anti-Adalimumab.

2. Samples, positive controls and standards incubation

Add 100 µl of standards, diluted controls or samples.

Incubate for 40 minutes at room temperature (+18°C/+25°C).

Wash step:

Remove the content of the wells by rapid inversion.

Wash 3 times with 300µL of TDL buffer.

Dry the microplate by tapping it gently on an absorbent paper to eliminate the excess of liquid.

3. Incubation of biotinylated antibodies

Add 100µL of **specific** biotinylated antibodies in identified wells.

Incubate for 20 minutes at room temperature (+18°C/+25°C).

Wash step:

Remove the content of the wells by rapid inversion.

Wash 3 times with 300µL of dilution and washing buffer.

Dry the microplate by tapping it gently on an absorbent paper to eliminate the excess of liquid.

4. Incubation of Conjugate

Add 100µL of conjugate.

Incubate for 15 minutes at room temperature (+18°C/+25°C).

Wash step:

Remove the content of the wells by rapid inversion.

Wash 3 times with 300µL of dilution and washing buffer.

Dry the microplate by tapping it gently on an absorbent paper to eliminate the excess of liquid.

5. Incubation of Substrate

Add 100µL substrate into each well.

Incubate for 15 minutes at room temperature (+18°C/+25°C). Protect from light.

6. Stop of the reaction

Add 100µl of H_2SO_4 to each well.

7. Reading

Read the optical density of each well at 450nm within 30 minutes after stopping reaction.

RESULTS AND INTERPRETATION

A. Dosage of Adalimumab

- The OD of the standard 1 should be at least 0.8.
- The positive control value should be comprised to inthe range indicated on the vial label.
- Trace a *degree 4 polynomial standard curve or a 4PL standard curve*, with plotting the units of the 5 standard points (µg/mL) along the abscissa (X axis) and the corresponding OD values along the ordinate (Y axis).
- The Adalimumab value can be directly read on the curve.
- Samples with values greater than that of standard 1 may be diluted to obtain a more precise result. The number of units should be multiplied by the selected dilution.

B. Dosage of anti-Adalimumab

- The OD of the standard 1 should be at least 0.8.
- The positive control value should be comprised into the range indicated on the vial label.
- Trace the standard curve (polynomial curve), plotting the units of the 5 standard points (ng/mL) along the abscissa (X axis) and the corresponding OD values along the ordinate (Y axis).
- The anti-Adalimumab value can be directly read on the curve.
- Samples with values greater than that of standard 1 may be diluted to obtain a more precise result. The number of units should be multiplied by the selected dilution.

CHARACTERISTICS AND PERFORMANCE OF THE TEST

Limits of detection / threshold values

Estimated on healthy patient population:
- 150 samples for Adalimumab
- 134 samples for Anti-Adalimumab

Limit of detection Adalimumab	Limit of detection Anti-Adalimumab
0.3 µg/mL >95th percentile	10 ng/mL >95th percentile

Assay range

Adalimumab	Anti-Adalimumab
0.3 µg/mL - 20 µg/mL	10 ng/mL - 160 ng/mL

Interfering Substances Study

LISA-TRACKER Duo Adalimumab (Theradiag) was evaluated to assess potential interfering reactivity to other antibodies and interference :
- on samples completed with the following components: bilirubin (0.2 mg/mL), hemoglobin (2 mg/mL), triglycerides (10 mg/mL) and rheumatoid factors (1000 IU/mL).

⇨ Any interference was detected.

Cross reaction

LISA-TRACKER Duo Adalimumab (Theradiag) was evaluated to assess potential cross reactivity to other therapeutic anti-TNF (Infliximab, Certolizumab, Etanercept and Golimumab) or anti-CD20 antibodies (Rituximab).

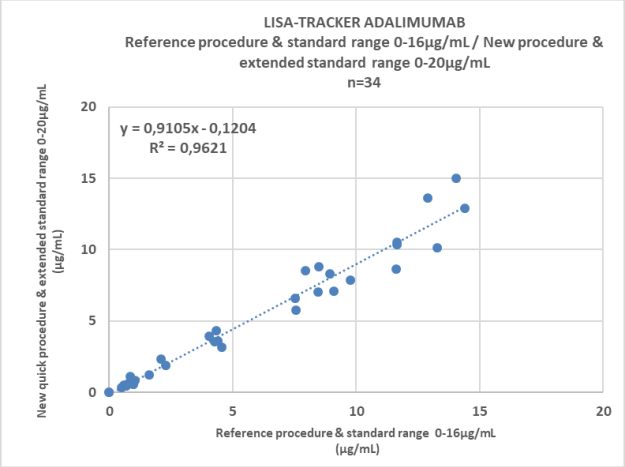
⇨ No cross reaction was detected.

Precision

	Intra-run 10 tests in a same assay		Inter-runs 2 tests 6 different assays	
Parameters	**Mean**	**CV (%)**	**Mean**	**CV (%)**
Adalimumab (µg/mL)	0.5	13.2	0.7	15.0
	7.5	4.5	8.2	10.3
	14.5	12.1	14.5	19.5
Anti-Adalimumab (ng/mL)	24	4.1	26	8.4
	65	2.9	73	11.1
	128	2.8	139	5.5

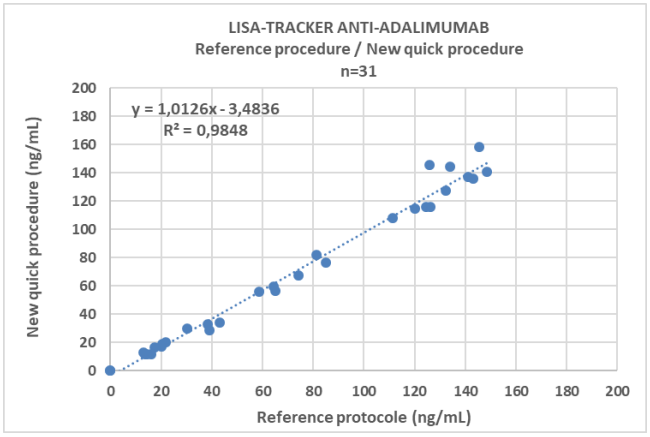
Correlation

The performances of the **Adalimumab determination obtained with the new quick procedure and extended standard range (0-20µg/mL)** were compared to the performances obtained with the reference procedure and standard range (0-16µg/mL).



=> A linear regression analysis of the two results showed that both are equivalent.

The performances of the **Anti-Adalimumab determination obtained with the new quick procedure** were compared to the performances obtained with the reference procedure.



=> A linear regression analysis of the two results showed that both are equivalent.

LIMITS

The presence of biotin in patients' specimens can potentially impact the immunodosages using the Streptavidin-Biotin technology.

QUALITY CONTROL

It is recommended to use internally and externally sourced control material for the different specificities. **IMMUNO-TROL Adalimumab** or **anti-Adalimumab** controls (Theradiag), Cat.n: LTA 002-PC or LTA 003-PC, contain **Adalimumab** or antibodies directed against **Adalimumab**. These materials are to be assayed in the same manner as the unknown samples.

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SUMMARY OF METHOD

A) Sample Dilution

Adalimumab	Anti-Adalimumab
1/201	1/2

B) Positive Control Dilution

Adalimumab	Anti-Adalimumab
1/201	1/2

C) Procedure

Reagents	Procedure
Standards	100µl / wells
Diluted positive controls	
Diluted samples	
Incubation	40 minutes at room temperature
Washing*	Wash 3 times with TDL buffer : 3 x 300µl / wells
Biotinylated antibodies	100µl / wells **(specific reagents)**
Incubation	20 minutes at room temperature
Washing*	Wash 3 times with TDL buffer : 3 x 300µl / wells
HRP-Streptavidin	100µl / wells
Incubation	15 minutes at room temperature
Washing*	Wash 3 times with TDL buffer : 3 x 300µl / wells
Substrate (TMB)	100µl / wells
Incubation	15 minutes at room temperature. Protect from light.
Stop solution	100µl / wells

***** ***Dry the microplate by tapping it gently on a towel to eliminate the excess of liquid.***

D) Configuration of the assays

a. 42 sera for Adalimumab and anti-Adalimumab

	1	2	3	4	5	6	7	8	9	10	11	12
A	**Standard 5**	Sera 3	Sera 11	Sera 19	Sera 27	Sera 35	**Standard 5**	Sera 3	Sera 11	Sera 19	Sera 27	Sera 35
B	**Standard 4**	Sera 4	Sera 12	Sera 20	Sera 28	Sera 36	**Standard 4**	Sera 4	Sera 12	Sera 20	Sera 28	Sera 36
C	**Standard 3**	Sera 5	Sera 13	Sera 21	Sera 29	Sera 37	**Standard 3**	Sera 5	Sera 13	Sera 21	Sera 29	Sera 37
D	**Standard 2**	Sera 6	Sera 14	Sera 22	Sera 30	Sera 30	**Standard 2**	Sera 6	Sera 14	Sera 22	Sera 30	Sera 30
E	**Standard 1**	Sera 7	Sera 15	Sera 23	Sera 31	Sera 39	**Standard 1**	Sera 7	Sera 15	Sera 23	Sera 31	Sera 39
F	**C+**	Sera 8	Sera 16	Sera 24	Sera 32	Sera 40	**C+**	Sera 8	Sera 16	Sera 24	Sera 32	Sera 40
G	Sera 1	Sera 9	Sera 17	Sera 25	Sera 33	Sera 41	Sera 1	Sera 9	Sera 17	Sera 25	Sera 33	Sera 41
H	Sera 2	Sera 10	Sera 18	Sera 26	Sera 34	Sera 42	Sera 2	Sera 10	Sera 18	Sera 26	Sera 34	Sera 42

Adalimumab assay

anti-Adalimumab assay

b. 2 sera for Adalimumab and anti-Adalimumab

	1	2	3	4	5	6	7	8	9	10	11	12
A	Standard 5	Standard 5										
B	Standard 4	Standard 4										
C	Standard 3	Standard 3										
D	Standard 2	Standard 2										
E	Standard 1	Standard 1										
F	**C+**	**C+**										
G	Sera 1	Sera 1										
H	Sera 2	Sera 2										

Adalimumab assay

anti-Adalimumab assay

c. 42 sera for anti-Adalimumab determination

	1	2	3	4	5	6	7	8	9	10	11	12
A	**Standard 5**	Sera 3	Sera 11	Sera 19	Sera 27	Sera 35						
B	**Standard 4**	Sera 4	Sera 12	Sera 20	Sera 28	Sera 36						
C	**Standard 3**	Sera 5	Sera 13	Sera 21	Sera 29	Sera 37						
D	**Standard 2**	Sera 6	Sera 14	Sera 22	Sera 30	Sera 30						
E	**Standard 1**	Sera 7	Sera 15	Sera 23	Sera 31	Sera 39						
F	**C+**	Sera 8	Sera 16	Sera 24	Sera 32	Sera 40						
G	Sera 1	Sera 9	Sera 17	Sera 25	Sera 33	Sera 41						
H	Sera 2	Sera 10	Sera 18	Sera 26	Sera 34	Sera 42						

anti-Adalimumab assay

SYMBOLS USED

CE	EC Declaration of conformity	▽	Number of test
	ELISA Test		Consult Instructions
REF	Catalogue number		Temperature limitation
LOT	Lot Number		Biological hazard
	Expiry Date	CONT NaN_3	Contains sodium azide
IVD	*In Vitro* Diagnostic Device	RCNS	Reconstitute with
	Manufacturer		Warning

Theradiag

IVD

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