CT application(s) summary report

- **Protocol title:** A Phase I, randomized, double-blind, 2-arm, parallel group trial to compare pharmacokinetics of Adessia with EU-authorized Humira in healthy male and female participants.
- **Protocol code number:** MP-ADA1-01
- **Eudra-CT:** 2022-003243-10
- **Version:** Final 2.0
- **Date:** 13 January 2023

- **Investigational Medicinal Product being tested:**

Biological ■ **Pharmaceutical** ☐ **Innovative** ☐

Herbal medicine ☐ **Medical device** ☐

- **Trade Name:** NA
- **IMP Authorization Status in Egypt:** not authorized
- **Pharmaceutical Form:** Solution for injection in prefilled syringe
- **Active Substance Name:** Adalimumab
- **Type:** Biological
- **IMPD Quality Dossier Decision:** Accepted

Date of Quality Administration: 01-August-2023

- **Sponsor:** Minapharm Pharmaceuticals and Chemical Industries S.A.E.
- **CRO:** CRS Clinical Research Services Berlin GmbH

- **Indication:** Bio similar adalimumab to the originator adalimumab (Humira), It is developed a treatment for the same marketed indications as Humira including rheumatoid arthritis, Polyarticular juvenile idiopathic arthritis, Enthesitis-related arthritis, Anklyosing spondylitis, Axial spondylitis, Axial spondyloarthriris without radiographic evidence of anklyosing spondylitis, Psoriatic arthritis, Plaque psoriasis, Hidradenitis suppurativa, Crohn's disease, Ulcerative colitis , Non-infectious uveitis among others.

- **Investigator's brochure (IB)**

Version: Final 1.0
Date: 10 November 2022

- **Name of all Sites:**

The trial is conducted in Germany (no available sites in Egypt).
1. Clinical Research Services CRS, Mannheim GmBH
2. Clinical Research Services CRS, Berlin GmBH

- **Name of PI(s):**

1. Dr. med. Jolanta Wierdak
2. Dr. Manuela Casjens

- **EDA approval date:** 10 August 2023.

- **Summary of pre-clinical studies:**

1) The similarity of Adessia to the reference product HUMIRA® was assessed by a comprehensive panel of **in vitro assays** that cover all relevant effector functions attributed to the Fab- and Fc-related pharmacology/mode of action of adalimumab.

--For appropriate pharmacological assessment, the comparative assessment between the proposed adalimumab biosimilar (Minapharm – Adalimumab product) and the reference product HUMIRA® (AbbVie) was based on upper and lower boundaries "corridor" that was established from testing 5 to 8 different batches of the reference product.

--The intended in-vitro functional similarity studies designed to include assays relevant to adalimumab pharmacological actions:

1. Fab-mediated functions:

-Cytokines are hormone-like proteins that allow cells to communicate, play critical roles in normal biologic processes, such as cell growth, inflammation and immunity. Tumor necrosis factor (TNF) is one of two inflammatory cytokines that are critical in the progression of inflammatory synovitis and articular matrix degradation, and therefore is a representative target for therapeutic intervention in rheumatoid arthritis.

-Adessia binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

- Neutralization of TNF-α in cell-based assay

The TNFα-neutralization assay is an assay designed to measure the adalimumab antigen-binding fragment (Fab) binding affinity against TNFα. Because of Fab binding, the TNFα-induced signal is decreased in relation to the concentration of the adalimumab used. The primary mechanism of action of adalimumab is the neutralization of circulating TNFα.

- Binding to target antigen (sTNF-α) ELISA

Another assay for assessing Fab mediated function is the sTNF- α binding ELISA, based on coating a 96 well immunoplate with HIS-tagged sTNF- α (antigen). The plate is then washed and blocked with PBS + 3% BSA, after which the dilutions of the analyte (Adessia) are added and bound to the antigen. Analyte binding is detected via TMB substrate reaction after addition and binding of POD-conjugated mouse anti-human IgG1 to antigen-bound analyte.

2. Fab- and Fc-mediated functions:

- Reporter gene ADCC (using membrane bound TNF-α cells CHO-K1)

Antibody-dependent cell-mediated cytotoxicity (ADCC) is a mechanism of action of antibodies through which virus-infected or other diseased cells are targeted for destruction by components of the cell-mediated immune system, such as natural killer cells. **ADCC is a primary mode of action of Adessia for killing target cells.** Adessia binds to target antigens on the cell surface (TNF α membrane bound cells; CHO-K cells).

3. Fc-mediated functions:

- Binding to complement (C1q) ELISA:

Adessia is capable of binding to the complement component C1q and initiating the classical complement pathway, leading to death of cells expressing tmTNF-α (membrane bound TNF- α).

4. Other Fc-mediated functions:

- Kinetics and binding assessment of representative isoforms of the relevant three Fc gamma receptors (FcγRs):

FcγRs bind to the Fc portion of IgG, and serve as a crucial link between humoral and cell mediated immune responses. Fcγ receptor plays a critical role in phagocytosis, endocytosis, antibody dependent

cellular cytotoxicity (ADCC), cytokine production, and enhancement of antigen presentation. In human, the classical FcγR family is divided into three receptor families (FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16)) based on structural homology, difference in affinity and differences in specificity for IgG subclasses.

- **FcγRI**
- **FcγRII (H variant)**
- **FcγRII (R variant)**
- **FcγRIII (V variant)**
- **FcγRIII (F variant)**

- Kinetics and binding assessment of Neonetal Fc receptor (FcRn)

FcRn has a role in prolonging the half-life of serum IgG. FcRn has the unique characteristic of binding to IgG in the acidic endosome and releasing IgG at the basic pH of systemic circulation. Through its interaction with IgG, FcRn contributes to the IgG homeostasis in the serum.

- The obtained results demonstrated high degree of similarity between the biosimilar and the originator. This was assessed in a comparative evaluation of functional properties: binding to an extensive range of Fc receptors which yielded highly similar results. This was also true for binding to the target TNF-α, cell-based TNF neutralization assay, as well as ADCC and complement C1q assay. Therefore, Adessia proved to be biosimilar to the reference product Humira with respect to all biological function parameters, where all results obtained for the Adessia drug product are found falling within the reference product corridor.
- **Adessia proved to be biosimilar to the reference product Humira with respect to all biological function parameters**, where all results obtained for the Adessia drug product are found falling within the reference product min-max and/or mean ± 3 SD corridor.

2) In addition to the proven biosimilarity from the in-vitro functional assays (in-vitro pharmacology), the absence of other critical risk factors that might require evaluation by in-vivo studies is confirmed in Adessia drug product (Minapharm – Adalimumab biosimilar).

- **Summary of previous clinical studies:** NA

- **Protocol:**

Phase: I ■ II III □ IV □

Objective(s):

Objectives	Endpoints
Primary	
• To test PK equivalence of MP adalimumab	• AUC0-inf • Cmax
Secondary	
• Comparison of PK parameters	• AUC0-last • Tmax, t1/2, Vz/F (Note: Vd specified as Vz/F)
• Assessment of immunogenicity	• Number and percentage of participants with anti-drug antibody (ADA) and neutralizing antibodies (nABs)
Other	

• Assessment of safety and tolerability (Including local tolerability)	• Number and percentage of participants with treatment emergent adverse events (TEAEs) • Number and percentage of participants with local reactions at the injection site after subcutaneous (s.c.) administration
• Comparison of further PK parameters • Assessment of further safety and tolerability aspects	• AUC_{ext}, t_{last}, λz, CL/F • Other safety parameters (safety laboratory, vital signs, and Electrocardiogram (ECG))

➢ Introduction

-Adalimumab **is a human monoclonal antibody** binding specifically to **tumor necrosis factor (TNF) alpha**, thereby neutralizing the biological function of the TNF pathway. TNF is involved in causing inflammation and found at high levels in patients with inflammatory diseases such as rheumatoid arthritis or Crohn's disease. By attaching to TNF, adalimumab **blocks its activity**, thereby **reducing inflammation** and other symptoms of the diseases.

Adalimumab is a disease-modifying antirheumatic drug.

Adalimumab was first approved in the United States in 2002, and in 2003 in the European Union under the trade name Humira. Since 2014, several biosimilars to Humira were developed and approved.

Adalimumab belongs **to the essential medicines** as listed by the World Health Organization.

➢ Background

-Adalimumab (Humira):

Humira is the originator product of adalimumab and is approved in the EU for several indications. Humira is given **as an injection under the skin**, usually **every 2 weeks**. The dose and frequency depend on the condition to be treated. After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being **reached about 5 days** after administration. The average **absolute bioavailability** of adalimumab estimated from 3 studies following a single 40 mg subcutaneous dose was 64%.

-MP-adalimumab biosimilar (Adessia):

It is produced in Chinese hamster ovary (CHO) cells is developed as **biosimilar to Humira**. It is developed for **the same treatments as Humira** including rheumatoid arthritis, psoriasis, Crohn's disease among others.

➢ Rationale:

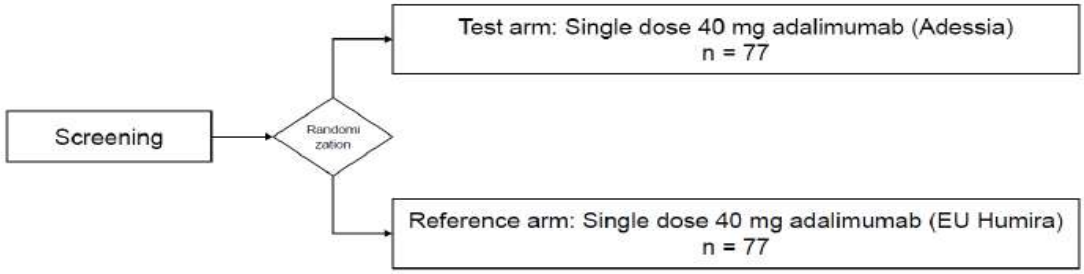
The sponsor develops a biosimilar adalimumab (Adessia) to **enhance availability** of this essential medicine. The development program of Adessia is planned to establish comparability of biosimilar adalimumab with the originator adalimumab (Humira), to ensure previously proven safety and efficacy of adalimumab is maintained.

The **purpose of this trial** is to compare pharmacokinetics (PK), safety, tolerability, and immunogenicity of Adessia and EU-approved Humira after a single s.c. injection of 40 mg.

➢ Design:

This Phase I trial will be conducted in a randomized, double-blind, single dose, 2-arm, parallel trial design in healthy male and female participants.

The trial will be performed in **2 parallel groups of 77 participants each**. The participants will be randomly assigned to trial intervention (test product: Adessia, or comparator product: EU Humira). The participants will receive **a single dose of 40 mg** of the trial intervention (either test or comparator product) as **subcutaneous injection** following a light, low-fat breakfast.



Written informed consent must be provided before any protocol-related procedures are performed. All participants will undergo a **screening examination within 28 to 2 days prior** to administration of trial intervention, in which eligibility of the participants will be assessed. Eligible participants will be included in the intervention period.

The **intervention period** will consist of **1 in-house period of 3 days with 2 overnight stays**, followed by **15 planned post treatment visits**. The participants will be **hospitalized** on the day prior to administration of the trial intervention and will **stay at the trial site** for at least 24 h after administration of trial intervention (from morning of Day -1 until morning of Day 2). Participants are **followed up for 9 weeks**. **The End of treatment (EoT) examination** will be performed on the **last visit (on Day 64).** **Blood sampling** for PK, nABs and ADAs will be collected from **pre-dose until 9 weeks after administration** of trial intervention. Safety parameters will be assessed from screening to EoT examination.

The **duration of trial participation for each participant** is estimated to be approximately **between 9 and 13 weeks**.

The total duration of the trial first participant first visit (FPFV) to last participant last visit (LPLV) is expected to be **approximately 21 weeks.**

- **Trial intervention:**

The trial interventions (treatments) to be administered during the trial are displayed in the below table:

Group	Product	Dose	Formulation	Route of administration	Frequency of administration	No. of participants to be treated
1 (Test)	Adalimumab (Adessia)	40 mg	40 mg/ 0.4 mL prefilled syringe	subcutaneous injection	Single dose	77
2(Reference)	Adalimumab (Humira)					77

Identity of trial intervention:

	Test	**Reference**
Name:	Adalimumab (Adessia)	Adalimumab (Humira)
Active ingredient:	Adalimumab	
Description:	0.4 mL single dose pre-filled syringe with 40 mg adalimumab	0.4 mL single dose pre-filled syringe with 40 mg adalimumab
Formulation	Solution for injection	
Strength or concentration:	100 mg/mL (40 mg/0.4 mL)	
Dose:	Single dose of 40 mg	

Mode of administration	Subcutaneous injection	
Manufacturer/Marketing Authorization Holder:	Minapharm Pharmaceuticals and Chemical Industries S.A.E., Egypt	AbbVie Deutschland GmbH & Co.KG, Germany

--Criteria for temporarily delaying Administration of Trial Intervention:

The following conditions may allow a participant to be started on trial intervention once the conditions have resolved and the participant is otherwise eligible:

• If Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test result is not available on Day -1, the following Day 1 may be postponed until the results are made available, but no longer than **by 48 h.**

- **Justification for dose**

The recommended dose for **adult patients with rheumatoid arthritis** is 40 mg adalimumab to be given as single dose every 2 weeks and the recommended dose for **adult patients with psoriasis** is 80 mg adalimumab as starting dose followed by 40 mg adalimumab to be given as single dose every 2 weeks (see SPC of Humira, 2021).

In this trial a **single dose of 40 mg** will be given to the participants. The same dose is used for the test and comparator product. **Single dose testing** is considered **adequate** to address the objectives of this trial.

- **Benefit/risk assessment**

Benefit assessment

This trial will be performed **in healthy participants** who **will not have direct health benefits** from participation in this trial.

Risk assessment

Potential risks that participants in this trial might be exposed to may arise from administration of the test or comparator product as outline**d in the tabular summary:**

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Adalimumab		
Mode of action of adalimumab (Immunomodulation by neutralizing the biological function of the TNF pathway)	Adalimumab can cross the placenta and may affect normal immune responses in the newborn.	Participating women of childbearing potential will be required to **use adequate contraception** to prevent pregnancy and continue its use for **at least 5 months after the last** Humira treatment Pregnant, lactating or breastfeeding women are **excluded from participation**
	By suppressing the immune reaction, the risk of infection or reaction to attenuated live vaccines is increased.	Participants will be **monitored for infections** during the trial. Volunteers with clinically relevant infections **within 30 days prior** to administration are excluded. Volunteers with

		infections requiring hospitalization or intravenous antibiotic treatment **within 6 months before** administration are **excluded** from participation
		Volunteers who had received **attenuated live vaccines within 4 weeks prior** to screening will be **excluded** from participation. During the study, vaccinations with **attenuated live vaccines** is **prohibited until EoT.** Other **vaccinations should be avoided from 2 weeks before until 2 weeks after** investigational medicinal product (IMP) administration
Allergic reactions to the trial intervention or excipients	Administration of an antibody might lead to a hypersensitive reaction.	Specific exclusion criteria have been defined *Known hypersensitivity to any trial intervention (active substances or excipients of the preparations) to be used in the trial. * Standard medical care to be applied.
Trial Procedures		
Complications from indwelling catheters	Local reactions, infections, nerve or tissue damage may occur (rare).	Standard medical care to be applied when catheters are used.
Allergic reactions to ECG electrodes or dressing adhesive	Local intolerance may occur (rare).	Standard medical care to be applied when catheters are used.

Overall benefit: Risk conclusion

The data to be obtained from this trial will **form the basis** for developing the **biosimilar** for the treatment of patients with rheumatoid arthritis, psoriasis, and Crohn's disease, and other indications of the reference drug.

The benefit/risk assessment will be **continuously monitored** during the conduct of this trial and will be updated in accordance to changes of COVID-19 pandemic situation and related authority regulations and recommendations.

The **importance of the objective** of this trial is considered **to outweigh the risks and burdens** to the participants. Measures are implemented to **minimize burdens and risks** for the participants.

The benefit/ risk assessment according to the German Drug Law (AMG, § 40, Abs 1, Nr. 2) is favorable and justifies the planned trial in healthy volunteers.

- **Pregnancy**

• Details of all pregnancies in female participants will be collected **until 5 months** after IMP administration and **up to 3 months** following the estimated delivery date.
• If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it **to the sponsor within 24 h** of learning of the participant's pregnancy.
• While pregnancy itself is **not considered** to be an Adverse event (AE) or Serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be **reported as an AE or SAE.**
• Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are **considered SAEs** and will be reported as such.
• The pregnant female participant will be followed to determine the outcome of the pregnancy. The investigator will **collect follow-up information** on the **pregnant female** participant and **the neonate**, and the information will be forwarded to the sponsor.
• Any **posttrial pregnancy-related SAE** considered reasonably related to the trial intervention by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of a SAE through spontaneous reporting.

➢ Interim analyses

No statistical interim analysis is planned.

• **Questions & Answers:**

	EDA Requirements	Company Comments
1	Specify and unify the targeted therapeutic inflammatory disease(s) as it is only mentioning the recommended doses for both Psoriasis and Rheumatoid Arthritis indications in section 4.3. Justification for dose.	Humira is used to treat a number of diseases such as Rheumatoid arthritis, Polyarticular juvenile idiopathic arthritis, Enthesitis-related arthritis, Ankylosing spondylitis, Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, Psoriatic arthritis, Plaque psoriasis, Hidradenitis suppurativa, Crohn's disease, Ulcerative colitis, Non-infectious uveitis. Adessia is intendend to be marketed for the same indications. **Kindly note** that the MP-ADA1-01 trial does not treat any disease. It is conducted on healthy participants for PK and safety evaluation. The selected dose of administration of 40 mg is within the therapeutic limits of adalimumab. Comparative biosimilar testing allows the extrapolation of data to cover the indications of the originator.
2	A clarification of the **protocol-prohibited medications** as no examples is mentioned.	Concomitant medication during the clinical trial coded MP-ADA1-01 is addressed in section 6.8 of the clinical protocol: "During the trial, no concomitant medications except hormonal contraception are allowed. In case of AEs, a symptomatic treatment (e.g., single doses of paracetamol or ibuprofen) will be given as necessary."

3	Regarding (Criteria for temporarily delaying Administration of Trial Intervention) in page 30: "The following conditions may allow a participant to be started on trial intervention once the conditions have resolved and the participant is otherwise eligible". There is only one condition is mentioned.	The wording in section 5.5 of the clinical protocol may be slightly imprecise as there is indeed only one condition temporarily delaying the administration of trial intervention. The content of this section is complete and correct.
4	A clarification about the meaning of **part dose** mentioned in section 6.4 in protocol (Doses will be categorized as "full dose", "part dose", or "no dose").	It is correct that the clinical protocol categorizes three doses: full dose, part dose and no dose. The dose of trial intervention and participant identification will be confirmed and documented at the time of dosing by an unblinded member of the site staff. "Part dose" describes any incomplete administration of a prefilled syringe of Adessia or Humira. A "part dose" will be considered a protocol deviation and documented as such.

- **Abbreviation:**

ADA	anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AUC	Area under the curve
CHO	Chinese hamster ovary
CL/F	Apparent clearance
Cmax	Maximum serum concentration
CRO	Contact research organization
CT	Clinical trail
COVID-19	Coronavirus disease 2019
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
EoT	End of treatment
EU	European Union
FPFV	first participant first visit
IgG	Immunoglobulin G
IMP	investigational medicinal product
LPLV	last participant last visit
nABs	neutralizing antibodies
PBS	Phosphate buffer saline
PI	Principal investigator
PK	pharmacokinetics
S.C.	subcutaneous
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPC	Summary of product characteristics

TEAEs	treatment emergent adverse events	
Tmax	Time to peak drug concentration	
TMB	3,3,5,5-Tetramethylbenzidine	
TNF	tumor necrosis factor	