NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY
FOR FACILITATED REGISTRATION PATHWAY (FRP)
Reference drug regulatory agency: European Medicines Agency (EMA)

PRODUCT NAME:
Yuflyma® 10mg/0.1ml Solution for Injection in pre-filled pen (MAL24056003AZ)

ACTIVE INGREDIENT:
Adalimumab 100 mg/ml

PRODUCT REGISTRATION HOLDER:
Celltrion Healthcare Malaysia Sdn. Bhd.

PRODUCT MANUFACTURER:
Celltrion, Inc., Incheon, South Korea

APPROVAL DATE:
2 May 2024 (DCA 396)

1.0 BACKGROUND INFORMATION

- Yuflyma is a biosimilar product to the reference product, Humira (contains adalimumab, a tumour necrosis factor alpha [TNF-α inhibitors]) manufactured by Abbvie Biotechnology GmbH, Germany.
- The assessment for this product was based on the *Guidance Document and Guidelines for Registration of Biosimilars in Malaysia* and the *EMA Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance*, which focused on demonstrating similarities between the biosimilar product (Yuflyma) and its reference product (Humira) in terms of quality, efficacy, and safety. This was achieved through head-to-head comparisons in analytical, non-clinical, and clinical studies between the biosimilar product and the reference product. Following the reliance and risk-based approach, the assessment also focused on verification of the sameness between what has been approved by the chosen reference agency (EMA) and the dossier submitted, except for Malaysian-specific requirements, particularly the labelling for biosimilar products and risk minimization to be implemented in Malaysia.

1.1 Approved Indications

Rheumatoid Arthritis
Yuflyma is indicated for reducing signs and symptoms, inducing major clinical response and clinical remission, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
Yuflyma can be used alone or in combination with methotrexate or other disease modifying anti-rheumatic drugs (DMARDs).

Psoriatic Arthritis
Yuflyma is indicated for reducing the signs and symptoms of active arthritis in patients with psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
Yuflyma can be used alone or in combination with disease modifying anti-rheumatic drugs.

Axial Spondyloarthritis
Ankylosing Spondylitis
Yuflyma is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Non-radiographic Axial spondyloarthritis (Axial Spondyloarthritis without radiographic evidence of AS)
Yuflyma is indicated for reducing signs and symptoms in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Plaque Psoriasis
Yuflyma is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Crohn's Disease
Yuflyma is indicated for the treatment of moderately to severely active Crohn's Disease in adult patients who have inadequate response to conventional therapy. Yuflyma is also indicated for treatment in adult patients with moderately to severely active Crohn's Disease who have lost response to or are intolerant to infliximab.

Ulcerative colitis
Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Hidradenitis Suppurativa
Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

Uveitis
Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid- sparing, or in whom corticosteroid treatment is inappropriate.

Paediatrics

Juvenile idiopathic arthritis
Polyarticular Juvenile Idiopathic Arthritis
Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients aged above 2 years old who had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis
Yuflyma is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Paediatric Crohn's Disease
Yuflyma is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and/or an immunomodulator, or who are intolerant to or have contraindication for such therapies.

Paediatric Plaque Psoriasis
Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Paediatric Uveitis
Yuflyma is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

Adolescent hidradenitis suppurativa
Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa (HS) therapy.

Pediatric Ulcerative Colitis
Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in patients aged 6 years and above who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

1.2 Approved Posology

Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis (Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis)
The recommended dose of Yuflyma for adult patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or other DMARDs may be continued during treatment with Yuflyma.
In rheumatoid arthritis, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of Yuflyma to 40 mg every week or 80 mg every other week. (optional).

Plaque Psoriasis
The recommended dose of Yuflyma for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.
Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.
Beyond 16 weeks, patients with inadequate response to Yuflyma 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage. If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week.

Crohn's disease
The recommended Yuflyma induction dose regimen for adult patients with severe Crohn's Disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (dose can be administered as 160 mg in one day or as 80 mg per day for two consecutive days), 80 mg at week 2, can be used with the awareness that the risk for adverse events is higher during induction.
After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Yuflyma and signs and symptoms of disease recur, Yuflyma may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

Some patients who experience decrease in their response may benefit from an increase in dosage to 40 mg Yuflyma every week or 80 mg every other week.

Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Ulcerative Colitis
The recommended Yuflyma induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection.

Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with Yuflyma. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.
Some patients who experience decrease in their response may benefit from an increase in dosage to 40 mg Yuflyma every week or 80 mg every other week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Adalimumab should only be continued in patients who have responded during the first 8 weeks of therapy.

Hidradenitis Suppurativa
The recommended Yuflyma dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as 160 mg in one day or as 80 mg per day for two consecutive days), followed by 80 mg two weeks later at Day 15. Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week. Antibiotics may be continued during treatment with Yuflyma if necessary.

Should treatment need to be interrupted, Yuflyma may be re-introduced.

In patients without any benefit after 12 weeks of treatment, prescriber should consider to discontinue the treatment.

Uveitis
The recommended dose of Yuflyma for adult patients with uveitis is an initial dose of 80mg, followed by 40mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with Yuflyma alone. Treatment with Yuflyma can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Yuflyma.

Paediatric

Juvenile idiopathic arthritis
Polyarticular juvenile idiopathic arthritis
The recommended dose of Yuflyma for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table 1). Yuflyma is administered every other week via subcutaneous injection.

Table 1. Adalimumab dose for patients with Polyarticular Juvenile Idiopathic Arthritis

Patient Weight	Dosing Regimen
10 kg to < 30 kg	-
≥ 30 kg	40 mg every other week

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

Adalimumab has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of adalimumab in patients aged less than 2 years for this indication.

Enthesitis-related arthritis
The recommended dose of Yuflyma for patients from 6 years of age with enthesitis-related arthritis is based on body weight (Table 2). Yuflyma is administered every other week via subcutaneous injection.

Table 2. Adalimumab Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥ 30 kg	40 mg every other week

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

Adalimumab has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Paediatric Crohn's disease
The recommended dose of Yuflyma for patients from 6 to 17 years of age with Crohn's disease is based on body weight (Table 3). Yuflyma is administered via subcutaneous injection.

Table 3. Adalimumab Dose for Paediatric Patients with Crohn's Disease

Patient weight	Induction dose	Maintenance dose starting at week 4
< 40 kg	• 40 mg at week 0 and 20 mg at week 2 * In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 80 mg at week 0 and 40 mg at week 2	–
≥ 40 kg	• 80 mg at week 0 and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 160 mg at week 0 (dose can be administered as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at week 2.	40 mg every other week

* Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus,it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

Patients who experience insufficient response may benefit from an increase in dosage:
• ≥ 40 kg: 40 mg every week or 80 mg every other week

Continued therapy should be carefully considered in a subject not responding by week 12.
There is no relevant use of adalimumab in children aged less than 6 years for this indication.

Paediatric plaque psoriasis
The recommended Yuflyma dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 4). Yuflyma is administered via subcutaneous injection.

Table 4. Adalimumab Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with adalimumab is indicated, the above guidance on dose and treatment duration should be followed.

The safety of adalimumab in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.

There is no relevant use of adalimumab in children aged less than 4 years for this indication.

Paediatric uveitis
The recommended dose of Yuflyma for paediatric patients 2 years of age and older with chronic non- infectious uveitis is based on body weight (Table 5). Yuflyma is administered via subcutaneous injection.

In paediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with methotrexate.

Table 5. Adalimumab Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	-
≥ 30 kg	40 mg every other week in combination with methotrexate

Note: Yuflyma is available as 40 mg presentations or 80 mg presentations. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose.

When Yuflyma therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of an adalimumab loading dose in children < 6 years of age (see section 5.2).

There is no relevant use of adalimumab in children aged less than 2 years in this indication.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis (see section 5.1).

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)
There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa (HS). The posology of adalimumab in these patients has been determined from pharmacokinetic modeling and simulation.

The recommended Yuflyma dose in adolescent patients from 12 years of age weighing at least 30 kg with hidradenitis suppurativa is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

Yuflyma may be available in different strengths and/or presentations.

In adolescent patients with inadequate response to Yuflyma 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

Antibiotics may be continued during treatment with Yuflyma if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Yuflyma.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, Yuflyma may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated.

There is no relevant use of Yuflyma in children aged less than 12 years in this indication.

Paediatric ulcerative colitis
The recommended dose of Yuflyma for patients from 6 to 17 years of age with ulcerative colitis is based on body weight (Table 6). Yuflyma is administered via subcutaneous injection.

Table 6. Adalimumab Dose for Paediatric Patients with Ulcerative Colitis

Patient weight	Induction dose	Maintenance dose starting at week 4*
< 40 kg	• 80 mg at week 0 and • 40 mg at week 2	• 40 mg every other week
≥ 40 kg	• 160 mg at week 0 and • 80 mg at week 2	• 80 mg every other week

*Paediatric patients who turn 18 years of age while on Yuflyma should continue their prescribed maintenance dose.

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

There is no relevant use of adalimumab in children aged less than 6 years in this indication.

1.3 Route of Administration
Subcutaneous

1.4 Pharmacological Aspects

Pharmacodynamic Properties

Mechanism of action

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis (Ps) plaques. In plaque psoriasis, treatment with Humira may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which Humira exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF,including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 1-2 X 10^{-10}M).

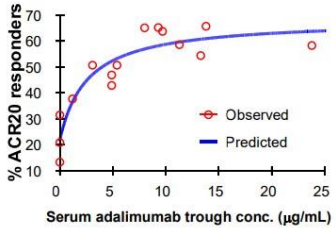
Pharmacodynamic effects

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and serum cytokines (IL-6) was observed compared to baseline in patients with RA. A decrease in CRP levels was also observed in patients with JIA, Crohn's disease, ulcerative colitis and hidradenitis suppurativa as well as a significant reduction in the expression of TNF and inflammatory markers such as human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon of patients with Crohn's disease.

Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration. Patients with RA, PsA and AS often experience mild to moderate anemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet counts. Patients treated with adalimumab usually experienced improvement in these hematological signs of chronic inflammation.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{max} equation as shown below:

Figure 1: Concentration-Efficacy Relationship



EC_{50} estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic/pharmacodynamic modeling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase II and III trials.

Pharmacokinetic Properties

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab was slow, with mean peak serum

concentration being reached about five days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%.

Distribution and Elimination
The single dose pharmacokinetics of adalimumab were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (Vss) ranged from 4.7 to 6.0 L, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-state pharmacokinetics
Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of approximately 5 mcg/mL (without concomitant methotrexate (MTX) and 8 to 9 mcg/mL (with concomitant MTX), respectively. The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week SC dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

In patients with psoriasis, the mean steady-state trough concentration was 5 mcg/mL during adalimumab 40 mg eow without concomitant methotrexate treatment.

In patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8mcg/mL at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 mcg/mL during adalimumab 40 mg every week treatment.

In patients with uveitis, a loading dose of 80mg adalimumab on Week 0 followed by 40mg adalimumab every other week starting at Week 1, result in mean steady-state concentrations of approximately 8 to 10 mcg/mL.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, adolescent patients with HS, and pediatric patients ≥ 40 kg with CD).

Population pharmacokinetic analyses with data from over 1200 patients revealed that coadministration of MTX had an intrinsic effect on adalimumab apparent clearance (CL/F) (see DRUG INTERACTIONS). As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

Other more minor factors were also identified; higher apparent clearance was predicted in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

In patients with Crohn's disease, the loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves mean serum adalimumab trough levels of approximately 12 mcg/mL at Week 2 and Week 4. Mean steady-state trough levels of approximately 7mcg/mL were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg adalimumab every other week.

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12 mcg/mL during the induction period. Mean steady-state trough levels of approximately 8 mcg/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.

Special Populations
Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Geriatrics
Age appeared to have a minimal effect on adalimumab apparent clearance. From the population analyses, the mean weight-adjusted clearances in patients 40 to 65 years (n=850) and ≥65 years (n=287) were 0.33 and 0.30 mL/h/kg, respectively.

Paediatrics
Following the administration of 24 mg/m2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/mL (102 % CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 µg/mL (47.7% CV) with concomitant methotrexate. The mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.6 µg/mL and 8.1 µg/mL, respectively. In patients with polyarticular juvenile idiopathic arthritis (JIA) who were 2 to <4 years old or aged 4 and above weighing <15kg dosed with adalimumab 24 mg/m2, the mean trough steady-state serum adalimumab concentrations w a s 6.0 ± 6.1µg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 µg/ml (71.2% CV) with concomitant methotrexate.

Following the administration of 24 mg/m2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/mL for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/mL with concomitant methotrexate.

In paediatric patients with moderately to severely active Crohn's disease, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomized 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7±6.6 µg/mL for patients ≥ 40 kg (160/80 mg) and 10.6±6.1 µg/mL for patients < 40 kg (80/40 mg).

For patients who stayed on their randomized therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5±5.6 µg/mL for the Standard Dose group and 3.5±2.2 µg/mL for the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3±11.4 µg/mL (40/20 mg, weekly) and 6.7±3.5 µg/mL (20/10 mg, weekly).

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 µg/mL (79% CV).

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, pediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule of 40 mg every other week is predicted to provide serum adalimumab exposure similar to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week.

Following the subcutaneous administration of body weight-based dosing of 0.6 mg/kg (maximum of 40 mg) every other week to pediatric patients with ulcerative colitis, the mean trough steady-state serum adalimumab concentration was 5.01±3.28 µg/mL at Week 52. For patients who received 0.6 mg/kg (maximum of 40 mg) every week, the mean (±SD) trough steady-state serum adalimumab concentration was 15.7±5.60 µg/mL at Week 52.

Gender
No gender-related pharmacokinetic differences were observed after correction for a patient's body weight.

Race
No differences in immunoglobulin clearance would be expected among races. From limited data in non- Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic and Renal Insufficiency
No pharmacokinetic data are available in patients with hepatic or renal impairment.

Disease States
Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

- Yuflyma drug substance is a recombinant human monoclonal IgG1 antibody subclass. It is a glycoprotein with one N-linked glycosylation site in the CH2 domain of each heavy chain. The molecular formula for the heavy and light chains are $C_{2197}H_{3404}N_{584}O_{678}S_{15}$ and $C_{1027}H_{1610}N_{282}O_{332}S_6$, respectively.
- The active substance is produced in Chinese Hamster Ovary (CHO) cells. The manufacturing process consists of inoculum expansion, production and harvest (upstream process), and purification (chromatography), filtration and filling into bottles (downstream process). The manufacturing process has been described accordingly and considered to be satisfactory.
- The DS upstream and downstream processes have been validated and have been demonstrated to consistently produce drug substances meeting its pre-defined acceptance criteria.
- The manufacturing process of DS contains raw materials derived from either bovine and/or porcine. Dialysed foetal bovine serum (FBS) and trypsin-EDTA (porcine pancreas, bovine lactose) were used during cell line development. All animal derived raw materials used at CELLTRION for the production of DS is in compliance with the EMA "Note for guidance on minimizing the risk of transmitting animal encephalopathy agents via medicinal products". Risk of transmissible spongiform encephalopathy (TSE) contamination of each animal origin material has been evaluated and the risk is considered negligible.
- The data from stability studies support the proposed shelf life of DS is 48 months when stored at -75±15°C.
- Good Manufacturing Practice (GMP) compliance for the drug substance manufacturer was verified by the Ministry of Food and Drug Safety, Korea.

2.1.2 Finished Product

- The finished product manufacturing process consists of formulation, sterile filtration, aseptic filling, visual inspection, labelling and assembly.
- The manufacturing process steps were validated using four consecutive drug product lots. Manufacturing process validation data for hold times and assembly of the final finished product were provided. All process validation results were within acceptance limits.
- The specification of finished product includes clarity, colour, visible particles, pH, extractable volume, osmolality, sub-visible particles, safety (endotoxin, and sterility), identity, purity/impurity, protein concentration, potency and functionality test.
- The proposed shelf life of drug product stored at 2 - 8°C is 36 months. Stability data for long term storage at 2-8°C for 36 months, accelerated conditions at 25±2°C/60±5% RH for 6 months and stress conditions at 40±2°C/75±5 % RH have been submitted to support the proposed storage condition. The results of photostability study indicate that the drug product is photo-stable when stored in its secondary packaging.
- Yuflyma is presented as a single-use sterile liquid solution for administration via subcutaneous (SC) in a pre-filled syringe (PFS), PFS with safety guard (PFS-S) or auto-injector (AI) intended to deliver 40 mg (0.4ml) or 80mg (0.8ml) of adalimumab solution at a concentration of 100 mg/ml.
- Endorsement letter for the auto-injector device had been issued by Medical Device Authority. (Dated: 16 March 2023)
- Excipients: Acetic Acid and Sodium Acetate Trihydrate (buffering agent), glycine (stabilizer), Polysorbate 80 (surfactant) and water for injection (solvent).
- The product has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 (R1) guidelines.
- Good Manufacturing Practice (GMP) compliance for the drug product manufacturer was verified by the Federal Agency for Medicines and Health Products, Belgium.

2.1.3 Comparability Studies of Quality

- A comprehensive similarity exercise following the principles outlined in the committee for medicinal products for human use (CHMP) guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance (quality issues) has been performed. The comparability studies have been done by analysing 10 lots of Yuflyma (including 6 finished product and 4 active substance batches produced at the commercial scale) and 10 lots of Humira, side-by-side with qualified state-of-the-art physicochemical and biological methods. The statistical quality range was defined as estimated mean of Humira ± 3 x standard deviation. All methods and biological assays used for similarity assessment have been validated as defined in ICH Q2 (R1).
- A high similarity between Yuflyma and Humira has been demonstrated for the following physicochemical (for detailed structural heterogeneity and purity/impurity studies) and biological properties (for evaluation of functional assays, potency and binding affinity related to putative MOA): primary and higher order structure, content and extractable volume, size heterogeneity, large variants (with some minor exceptions), glycan profiles, binding to soluble and transmembrane TNFα and neutralisation of TNFα, reverse signaling activity, binding to Fc-receptors (FcγRIIIa [V, F], FcγRIIIb, FcγRIIa, FcγRIIb, FcγRI and FcRn), binding to C1q and CDC activity, ADCC activity, inhibition of TNFα-induced apoptosis, IL-8 and VCAM-1 release, induction of regulatory macrophages and subsequent T-cell anti-proliferation.
- All the minor differences (glycosylation, charged variants, primary structure) observed have been adequately justified. On the basis of the totality of evidence, Yuflyma is considered to be comparable to EU-Humira notwithstanding minor differences that are unlikely to have a clinical impact.
- In addition to the similarity assessment, comparative stability tests under accelerated and stress conditions were conducted to support the similarity. Both Yuflyma and EU-approved

Humira showed similar trends in intact IgG by CE-SDS (non-reduced) and in main peak by IEC-HPLC, as well as an upward trend in the acidic group by IEC-HPLC, suggesting that the stability profiles of Yuflyma and Humira are similar. In the forced degradation studies under oxidative stress, UV stress, high temperature stress, and high pH stress conditions, the data further support the similarity of Yuflyma and Humira.

- The full set of biosimilarity data at quality level presented is considered appropriate and biosimilarity of Yuflyma to Humira has been demonstrated.

2.2 Comparability Studies of Non-Clinical

- Non-clinical studies comprised of stepwise risk-based comparative in vitro analyses of biological activity (binding to target antigen(s), binding to representation isoforms, Fab and Fc associated functions
- Besides, an OECD GLP-compliant, 28-day repeat-dose toxicity and toxicokinetic study in cynomolgus monkeys was conducted.
- Yuflyma was compared to Humira-EU (10 lots each) in the in vitro studies.
- Comprehensive biological assays conducted, demonstrated the similar Fab-related biological activities of Yuflyma and Humira-EU engaging with its target TNFα, and the Fc-based functionalities. The glycan profiles were similar. Only some minor variations were observed in the high mannose and afucosylation contents. Yuflyma had slightly higher total afucosylation contents being 8.08 % ± 0.7 than Humira-EU (6.80 % ± 0.6), but this did not result in differences in the Fc-related functions (binding to FcγRIIIa and ADCC activity).
- Overall, the functional in vitro data demonstrate, that Yuflyma and Humira-EU are similar, and no quality (e.g. molecular structure, glycosylation profile) or non-clinical (e.g. target receptor binding, functional activity) differences were found that would likely have an impact on the efficacy and/or safety/immunogenicity of the Yuflyma in comparison to the Humira-EU.
- The additional biological assays which were done to support the extrapolation to other indications (including inflammatory bowel disease), indicated that Yuflyma and Humira-EU had similar effects on inhibition of TNFα- induced apoptosis, IL-8 and VCAM-1 release, regulatory macrophage induction and subsequent T-cell anti-proliferation.
- The local tolerance and antigenicity assessments were included in the repeated-dose toxicity study. Only one female at 32 mg/kg Yuflyma and one female at 32 mg/kg Humira-EU group on Day 29 was detected positive for anti-drug antibodies. The anti-drug-antibody formation did not affect the serum concentration-time profiles on Day 22.
- Stand-alone safety pharmacology, in vivo pharmacodynamics, secondary pharmacodynamics, pharmacodynamic drug interactions, reproductive and developmental toxicity, genotoxicity, carcinogenicity studies were not conducted and are not required for biosimilar products.
- The provided data supported the conclusion that Yuflyma can be considered biosimilar to the reference product EU-Humira from the non-clinical pharmacology point of view.

2.3 Comparability Studies of Clinical

To further support the biosimilarity of Yuflyma to Humira, the following five clinical studies have been conducted:

No.	Study	Title
1.	CT-P17 1.1 (pivotal)	A phase 1, randomized, double-blind, three-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of Yuflyma and Humira (US-licensed Humira and EU-approved Humira) in healthy subjects
2.	CT-P17 1.2 (supportive)	A pilot phase 1, randomized, double-blind, two-arm, parallel group, single-dose study to evaluate the safety and pharmacokinetics of Yuflyma and Humira in healthy male subjects
3.	CT-P17 1.3 (supportive)	A phase 1, randomized, open-label, two-arm, parallel group, single-dose study to compare the pharmacokinetics and safety of the Auto-Injector (AI [Pre-Filled Pen (PFS)] and Pre-filled Syringe (PFS) of Yuflyma in healthy subjects

4.	CT-P17 3.1 (pivotal)	A randomized, active-controlled, double-blind, phase 3 study to compare efficacy and safety of Yuflyma with EU-approved Humira when co-administered with methotrexate in patients with moderate to severe active rheumatoid arthritis (RA)
5.	CT-P17 3.2 (supportive)	A phase 3, open-label, single-arm, multiple-dose study to evaluate usability of subcutaneous Auto-Injector (AI) of Yuflyma in patients with moderate to severe active rheumatoid arthritis (RA)

2.3.1 Pharmacokinetics (PK)

Pharmacokinetics data were generated in the following four clinical studies i.e., CT-P17 1.1, CT-P17 1.2, CT-P17 1.3 and CT-P17 3.1. The data of each finding have been summarized below:

CT-P17 1.1

A total of 312 subjects were randomly assigned to one of 3 treatment groups in a 1:1:1 ratio. In each treatment group, all subjects received a single dose (40 mg) of either Yuflyma, US-Humira, or EU-Humira by SC injection via PFS on Day 1 followed by 10 weeks (70 days). The three primary PK endpoints of the study were AUC0-inf, AUC0-last, and Cmax. The overall study designs are acceptable and compliant with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010).

Table 3 Study CT-P17 1.1: Statistical Analysis of Primary PK Parameters for Adalimumab by Treatment (ANCOVA, PK Population)
Table 4 Study CT-P17 1.1: Statistical Analysis of Primary PK parameters of Adalimumab in (ANCOVA) (All Subjects Who Received a Full Dose)

PK Parameter (units)	Treatment	n	Geometric LS means[(a)]	Treatment comparison	Ratio (%) of geometric LS means[(a)]	90% CI[(a)]
$AUC_{0\text{-}inf}$ (h.µg/ml)						
Table 3	Yuflyma	80	2165.0	Yuflyma vs. EU-Humira	98.00	(90.06, 106.63)
	US-Humira	86	2046.5	Yuflyma vs. US-Humira	105.79	(97.17, 115.16)
	EU-Humira	89	2209.3	US-Humira vs. EU-Humira	92.63	(85.29, 100.61)
Table 4	Yuflyma	96	2248.7	Yuflyma vs. EU-Humira	102.16	(93.41, 111.74)
	EU-Humira	100	2201.1	Yuflyma vs. US-Humira	111.06	(101.39, 121.65)
	US-Humira	93	2024.8	US-Humira vs. EU-Humira	91.99	(84.05, 108.66)
$AUC_{0\text{-}last}$ (h.µg/ml)						
Table 3	Yuflyma	96	1949.2	Yuflyma vs. EU-Humira	100.79	(92.42, 109.92)
	US-Humira	93	1816.6	Yuflyma vs. US-Humira	107.30	(98.29, 117.13)

	EU-Humira	98	1933.9	US-Humira vs. EU-Humira	93.93	(86.08, 102.50)
Table 4	Yuflyma	102	1813.0	Yuflyma vs. EU-Humira	98.21	(88.75, 108.66)
	EU-Humira	104	1846.1	Yuflyma vs. US-Humira	107.12	(96.77, 118.58)
	US-Humira	102	1692.4	US-Humira vs. EU-Humira	91.68	(82.86, 101.43)
C_{max} (µg/ml)						
Table 3	Yuflyma	96	3.008	Yuflyma vs. EU-Humira	100.05	(93.69, 106.85)
	US-Humira	93	2.952	Yuflyma vs. US-Humira	101.89	(95.33, 108.89)
	EU-Humira	98	3.006	US-Humira vs. EU-Humira	98.20	(91.91, 104.92)
Table 4	Yuflyma	102	2.941	Yuflyma vs. EU-Humira	98.29	(91.85, 105.18)
	EU-Humira	104	2.993	Yuflyma vs. US-Humira	102.72	(95.96, 109.95)
	US-Humira	102	2.863	US-Humira vs. EU-Humira	95.68	(89.42, 102.39)

LS: Least squares.
Note: An analysis of covariance was performed with the natural log-transformed PK parameters as the dependent variable, treatment as a fixed effect and gender (male or female), Day -1 body weight, and study center as covariates.
$AUC_{0\text{-inf}}$ values in Table 3 were excluded from the statistical analysis after not meeting 1 or more of the following criteria: an adjusted correlation coefficient r^2 of ≥0.85 and a %AUCextp≤20%.
$AUC_{0\text{-inf}}$ values in Table 4 were excluded from the statistical analysis for subjects having less than 3 time points following C_{max} or $AUC_{0\text{-inf}}$ not calculable.
[a]The LS mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of geometric LS means and 90% CIs for the ratios.

Table 3 above showed the initial statistical analyses for AUC0-last, AUC0-inf and Cmax in which the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% when comparing Yuflyma with the reference product from EU as well as from US. Results for the additional analyses (Table 4) were in agreement with the initial analyses and supported the conclusion of biosimilarity.

Vast majority of subjects had anti-drug antibody (ADA) following the single adalimumab SC injection. The number of ADA negative subjects was 3 (3.1%), 5 (5.4%), 5 (5.0%) within Yuflyma, US-Humira, and EU-Humira treatment groups, respectively. An additional ANCOVA analysis was performed in subjects identified as having a positive ADA status and the 90% CIs of the geometric LSM ratios were within the predefined 80%-125% equivalence margin. Due to the small number of subjects who were negative for ADA, it was not possible to perform the ANCOVA analysis in this subset.

CT-P17 1.2

Study CT-P17 1.2 was a pilot study to evaluate the safety and PK of Yuflyma PFS and EU-Humira PFS. Limited PK data were collected as a secondary endpoint. PK results for study CT-P17 1.2 do not affect the overall assessment of biosimilarity.

CT-P17 1.3

A total of 193 subjects were randomly assigned to one of 2 treatment groups in a 1:1 ratio. In each treatment group, all subjects received a single dose (40 mg) of Yuflyma via either AI or PFS on Day 1, followed by 10 weeks (70 days). The three primary PK endpoints of the study were AUC0-inf, AUC0-last, and Cmax. The overall study designs are acceptable and compliant with the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" (EMA/CHMP/BMWP/403543/2010).

For AUC0-last, AUC0-inf and Cmax, the 90% confidence interval for the ratio of the AI and the PFS devices fell within the conventional acceptance range of 80.00-125.00%. Results for the additional analyses supported the conclusion of comparable pharmacokinetics between Yuflyma AI and Yuflyma PFS.

CT-P17 3.1

This study provided supportive comparative PK data (trough serum concentrations [Ctrough] as a secondary endpoint) following SC injections of 40 mg every 2 weeks of either Yuflyma or EU-Humira via PFS in combination with MTX in patients with moderate to severe active RA.

The mean Ctrough of adalimumab for both treatment groups in the PK population and by ADA status increased following the first doses and appeared to reach the plateau before week 22. In both Yuflyma and Humira treatment groups, patients with ADA had markedly lower Ctrough levels compared with patients without ADA. High ADA titer was also associated with lower Ctrough levels.

2.3.2 Pharmacodynamics (PD)

Validated PD markers do not exist for the efficacy of TNF-α inhibitors and therefore, no PD data were evaluated in the Phase 1 bioequivalence studies in healthy volunteers.

In the Phase 3 study (CT-P17 3.1), serum concentrations of Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (CCP), C-reactive protein (CRP), and Erythrocyte Sedimentation Rate (ESR) were assessed as secondary PD endpoints. The decreases in RF, anti-CCP, CRP and ESR levels in RA patients were similar up to Week 24 between Yuflyma and EU-approved Humira treatment groups.

2.3.3 Efficacy

In total, 648 patients with moderate to severe active RA were randomised as 1:1 to receive either Yuflyma (324 patients) or EU-Humira (324 patients) in Treatment Period I for 24 weeks. The study population was representative of RA patients in general and the treatment groups were well balanced in terms of basic demographic characteristics, disease duration, disease severity and use of concomitant medication. Then, in Treatment Period II, 303 patients who previously received Yuflyma continued the Yuflyma maintenance, while 305 patients who previously received EU-Humira were randomly assigned 1:1 to receive EU-Humira maintenance (153 patients) or switched to Yuflyma (151 subjects), respectively, for up to 48 weeks.

The primary efficacy endpoint was the proportion of patients achieving clinical response according to the ACR20 at Week 24 in the intent-to treat (ITT) population. Equivalence was defined as a 95% CI for the estimate of treatment difference entirely within the predefined equivalence margin of -15% to 15%.

Table 13 Proportion of Patients Achieving Response According to ACR20 at Week 24

Treatment Group	ACR20 Response Rate	Treatment Difference Estimate (%) [a]	95% CI of Treatment Difference (%) [a]
ITT Population			
Yuflyma	268/324 (82.72%)	0.00	(-5.94, 5.94)
EU-approved Humira	268/324 (82.72%)		
PP population			
Yuflyma	248/285 (87.02%)	0.06	(-5.60, 5.78)
EU-approved Humira	240/276 (86.96%)		

Abbreviations: ACR, American College of Rheumatology; ACR20, ACR 20% improvement criteria; CI, confidence interval; ITT, intent-to-treat; PP, per protocol. Note: Patients who terminated from the study prior to the week of interest, who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at the week of interest, and with incomplete data for evaluation of ACR20 criteria at the week of interest were considered as non-responder. a Estimate of the difference in proportion and 95% CI between the two treatment groups were estimated using the exact binomial method using a Farrington-Manning score method. Source: Post-text Table 14.2.2.1.

The sensitivity analysis rendered similar results. The 95% CI for the estimate of treatment difference estimated from the logistic regression using treatment group as a fixed effect, and country and disease activity by SDAI at screening as covariates was -5.75 to 5.86 for the ITT population and -5.07 to 5.93 for the PP population. Hence, the primary objective of this trial was met and the results were unchanged after controlling for country and disease activity.

ACR20 is considered an acceptable primary endpoint in the EMA Guideline on clinical investigation of medicinal products for the treatment of RA and it has been widely used in equivalence trials. However, while ACR20 at 6 months (24 week) is adequate for assessment of efficacy in non-inferiority trials, an earlier time point, before the therapeutic plateau is fully developed, is preferred in equivalence trials, to increase the sensitivity to detect possible differences. In addition to the primary efficacy endpoint of ACR20 response at week 24, the totality of data, including ACR20 response at all time-points, is thus considered important for the assessment of equivalence on clinical efficacy.

The predefined equivalence margin (EM) of -15% to 15% is in line with several previous adalimumab biosimilar processes and is acceptable. In equivalence trials, the PP (per-protocol) population is considered more conservative and the preferred population of analysis compared to ITT population, as stated in the ICH E9 Statistical Principles for Clinical Trials. Hence, the results for the PP population are considered even more relevant than the results for the primary ITT population.

The data from Study CT-P17 3.1 showed similarity between Yuflyma and Humira in both primary and secondary efficacy endpoints at Week 24. Similarity in efficacy was also supported by non-clinical PD data and was not significantly affected by antibody formation. Data from the second treatment period (Week 24 to 48) showed that efficacy was sustained up to week 52 in a comparable manner in all three treatment arms: Yuflyma and Humira maintenance groups as well as in patients who switched to Yuflyma at week 26. From the efficacy point of view, the claim for the biosimilarity between Yuflyma and Humira-EU is supported.

2.3.4 Safety

The safety data of Yuflyma were obtained from 1,166 subjects in 4 clinical studies (488 healthy male and female subjects [up to Day 71 in studies CT-P17 1.1 and 1.3], 30 healthy male subjects [up to Day 120 in study CT-P17 1.2] and 648 RA patients [up to Week 52 in study CT-P17 3.1]) who were exposed to at least one dose (full or partial) of Yuflyma, EU-Humira or US-Humira. Of these, 297 healthy subjects and 324 RA patients were exposed to Yuflyma.

The overall safety data from the confirmatory phase 3 study showed that 1,531 TEAEs were reported in 447 (69.0%) patients in the initial randomisation and 1,418 TEAEs in 416 patients in the second randomisation. The proportion of patients was similar between the Yuflyma and Humira treatment groups (218 [67.3%] and 229 [70.7%] patients, respectively), and among the Yuflyma maintenance, Humira maintenance and switched to Yuflyma groups (204 [67.3%], 105 [69.1%], and 107 [70.4%] patients, respectively). The majority of TEAEs were of grade 1 or grade 2 in intensity.

In conclusion, the safety profiles of Yuflyma and Humira were found similar in short-term and long-term use, up to 52 weeks. The data also shows sufficient similarity between Yuflyma and EU-Humira in terms of ADA formation, ADA titre levels, NAb formation and the impact of ADA formation on clinical parameters up to week 24. From the safety point of view, Yuflyma is therefore considered similar to Humira.

3.0 RISK MANAGEMENT PLAN (RMP)

- The applicant has submitted EU RMP version 1.0 dated 25 June 2020 which will be implemented in Malaysia.
- The routine risk minimisation measures of Yuflyma include:
    - Specific information, such as warnings, precautions, and advice on correct use, in the package insert addressed to patients and healthcare professionals
- Those measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below:
    - Important identified risks: Serious infections, Tuberculosis (TB), Malignancies, Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis [ON]) and BCG disease following live BCG vaccination in infants with in utero exposure to Yuflyma
    - Important potential risks: Progressive multifocal leukoencephalopathy (PML), Reversible posterior leukoencephalopathy syndrome (RPLS) and Adenocarcinoma of colon in ulcerative colitis (UC) patients
- In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.
- If important information that may affect the safe use of Yuflyma is not yet available, it is listed under ‘missing information’ below:
    - Missing information: Patients with immune compromised conditions, Long-term safety information in the treatment of children aged from 6 years to less than 18 years with Crohn’s disease (CD), Episodic treatment in psoriasis (Ps), ulcerative colitis (UC), and juvenile idiopathic arthritis (JIA) and Long-term safety information in the treatment of children with uveitis.

4.0 CONCLUSION

- Yuflyma has been developed as a biosimilar to the reference product, Humira. Comparative stepwise approach was used to demonstrate biosimilarity in terms of quality (structural, impurities and pharmaceutical properties), nonclinical (functional, pharmacologic and toxicology) and clinical (pharmacokinetic, efficacy and safety) between Yuflyma and Humira. Some minor differences were observed during the evaluation of analytical similarity which had been further assessed and determined to have no clinical impact.
- Similar efficacy, PK profile, immunogenicity and safety are demonstrated in clinical study between Yuflyma and Humira. No non-clinical safety findings were observed in repeat-dose toxicity study.
- The chosen RA population in the clinical study is considered as adequately sensitive and homogenous population to support biosimilarity in all sought of indications. The MOA of Humira is applicable to all approved indications, PK are linear, dose-proportional and relatively similar in all indications. Comprehensive set of studies in quality, non-clinical and clinical level support extrapolation to all indications of Humira.
- Based on the analytical, nonclinical and clinical data, all of which contribute to the totality of the evidence, Yuflyma is considered to be the biosimilar to Humira. Therefore, a benefit/ risk balance comparable to reference product can be concluded.
- All parts have been verified to be the same as what has been approved by the chosen reference agency (EMA), except for Malaysian-specific requirements, particularly the labelling of biosimilar products in Malaysia.
- Hence, Drug Control Authority (DCA) on the 396th meeting on 2nd May 2024 has decided to approve the registration of this product with the following indication:

Rheumatoid Arthritis
Yuflyma is indicated for reducing signs and symptoms, inducing major clinical response and clinical remission, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
Yuflyma can be used alone or in combination with methotrexate or other disease modifying anti-rheumatic drugs (DMARDs).

Psoriatic Arthritis
Yuflyma is indicated for reducing the signs and symptoms of active arthritis in patients with psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
Yuflyma can be used alone or in combination with disease modifying anti-rheumatic drugs.

Axial Spondyloarthritis
Ankylosing Spondylitis
Yuflyma is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Non-radiographic Axial spondyloarthritis (Axial Spondyloarthritis without radiographic evidence of AS)
Yuflyma is indicated for reducing signs and symptoms in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Plaque Psoriasis
Yuflyma is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Crohn's Disease
Yuflyma is indicated for the treatment of moderately to severely active Crohn's Disease in adult patients who have inadequate response to conventional therapy. Yuflyma is also indicated for treatment in adult patients with moderately to severely active Crohn's Disease who have lost response to or are intolerant to infliximab.

Ulcerative colitis
Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6- mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Hidradenitis Suppurativa
Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

Uveitis
Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid- sparing, or in whom corticosteroid treatment is inappropriate.

Paediatrics

Juvenile idiopathic arthritis
Polyarticular Juvenile Idiopathic Arthritis
Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients aged above 2 years old who had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis
Yuflyma is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Paediatric Crohn's Disease
Yuflyma is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and/or an immunomodulator, or who are intolerant to or have contraindication for such therapies.

Paediatric Plaque Psoriasis
Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Paediatric Uveitis
Yuflyma is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

Adolescent hidradenitis suppurativa
Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa (HS) therapy.

Pediatric Ulcerative Colitis
Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in patients aged 6 years and above who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.