NON-INTERVENTIONAL POST-AUTHORIZATION STUDY PROTOCOL

Study Title	Prospective, real-world cohort study to evaluate the effectiveness and safety of filgotinib for the treatment of patients with axial spondylo-arthritis, with a focus on early and long-term impact on pain and disease activity in routine clinical practice
Study Acronym	FIL-IMPACT (An Observational Study of FILgotinib IMpact on PAin and disease aCTivity in Axial Spondyloarthritis)
Protocol ID	AL0634/axSpA4003
Protocol Version:	2.0 Date: 21-Oct-2026
Amendment:	1
Registration Study ID	t.b.d.
Development Phase:	4
Active Substance:	Filgotinib
Medicinal Product:	Jyseleca Product Reference: EU/1/20/1480
Joint PASS:	No
Research Question and Objectives:	To assess the effectiveness and safety of newly initiated filgotinib in routine clinical practice in patients with axial spondyloarthritis, with a primary focus on early and sustained improvement in total spinal pain and additional evaluation of disease activity, patient-reported outcomes, treatment persistence, and safety
Countries:	Germany, Austria, UK, Ireland, The Netherlands, Belgium
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Confidentiality Statement

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2. LIST OF ABBREVIATIONS

AAU	acute anterior uveitis
ADR	adverse drug reaction
AE	adverse event
AEI	adverse events of interest
AS	ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
ASAS-HI	Assessment of Spondyloarthritis International Society health index
ASDAS	axial spondyloarthritis disease activity score
ASDAS-CRP	axial spondyloarthritis disease activity score based on c-reactive protein
axSpA	axial spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
bDMARD	biologic disease-modifying antirheumatic drug
BL	baseline
CI	confidence interval
CRF	case report form
CRP	c-reactive protein
d	day
DMARD	disease-modifying antirheumatic drug
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EMM	extra-musculoskeletal manifestation
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
ePRO	electronic patient-reported outcome(s)
FPFV	first patient first visit

GDPR	General Data Protection Regulation
GI	gastrointestinal
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HADS	hospital anxiety and depression scale
HLA-B27	human leukocyte antigen B27
IBD	inflammatory bowel disease
ICD-10	International Classification of Diseases, 10th Revision
ICF	informed consent form
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use
ICSR	individual case safety report
IEC	independent ethics committee
IL	Interleukin
IR	inadequate response
IRB	institutional review board
JAK	janus kinase
JAKi	janus kinase inhibitor
LEI	Leeds enthesitis index
LPLV	last patient last visit
MACE	major adverse cardiovascular event(s)
MAH	marketing authorization holder
MASES	Maastricht ankylosing spondylitis enthesitis score
MCII	minimum clinically important improvement
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mo	month(s)
NIS	non-interventional study
NMSC	non-melanoma skin cancer
nr-axSpA	non-radiographic axial spondyloarthritis
NRS	numeric rating scale

NSAID	non-steroidal anti-inflammatory drug
OLE	open label extension
PASS	patient acceptable symptom state
PDC	primary data collection
PhGA	physician global assessment
PMS	post-marketing surveillance
PRO	patient-reported outcome
PtGA	patient global assessment
PV	pharmacovigilance
q.d.	once daily
QoL	quality of life
r-axSpA	radiographic axial spondyloarthritis
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SJC	swollen joint count
SmPC	summary of product characteristics
SOP	standard operating procedure
SpA	spondyloarthritis
TJC	tender joint count
TNF	tumour necrosis factor
tsDMARD	targeted synthetic disease-modifying antirheumatic drug
WPI	Widespread Pain Index

3. RESPONSIBLE PARTIES

Not applicable for non-PASS NIS.

4. ABSTRACT

Study Title:
Prospective, real-world cohort study to evaluate the effectiveness and safety of filgotinib for the treatment of patients with axial spondyloarthritis , with a focus on early and long-term impact on pain and disease activity in routine clinical practice (FIL-IMPACT)

Protocol ID: AL0634/axSpA4003
Protocol Version: 2.0 Amendment 1
Date: 21 October 2026
Author: Els Kinable

Rationale and Background:
Axial spondyloarthritis (axSpA) is a chronic inflammatory disease associated with substantial burden due to pain, functional limitation, impaired quality of life, and socio-economic impact. Despite advances in treatment, a considerable proportion of patients experience insufficient response or intolerance to currently available therapies, including tumour necrosis factor (TNF) inhibitors and interleukin (IL)-17 inhibitors. Janus kinase (JAK) inhibitors represent an important therapeutic option targeting intracellular inflammatory pathways and may provide rapid symptom relief, particularly for pain. Filgotinib, an oral JAK1 preferential inhibitor, has demonstrated efficacy and safety in axSpA clinical trials, including the Phase 2 TORTUGA study and the ongoing Phase 3 OLINGUITO program and its open-label extension. However, randomised controlled trials are conducted under controlled conditions and may not fully reflect real-world clinical practice. There remains a need for prospective real-world evidence to characterize treatment effectiveness and disease activity control, especially early pain trajectories, multidimensional patient-reported outcomes, and treatment persistence across diverse healthcare settings.

Research Question:
To assess the effectiveness and safety of newly initiated filgotinib in routine clinical practice in patients with axSpA, with a primary focus on early and sustained improvement in total spinal pain and additional evaluation of disease activity, patient-reported outcomes, treatment persistence, and safety.

Objectives:
Primary

- Assess the absolute change from baseline in total spinal pain following initiation of filgotinib, with a specific focus on early improvements up to Month 3 and sustained or further improvement up to Month 24.

Secondary

- Evaluate the effect of filgotinib on disease activity (Axial Spondyloarthritis Disease Activity Score, ASDAS), including change from baseline and responder status, and examine the relationship between changes in spinal pain and changes in disease activity.

- Evaluate the effect of filgotinib on nocturnal spinal pain and mechanistic pain features, assessed by change from baseline in nocturnal spinal pain and in painDETECT and WPI scores, as well as by responder status (minimal clinically important improvement, MCII).

- Assess disease activity from the patient perspective by evaluating changes in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) total and item level scores, and their association with spinal pain outcomes.

- Examine the evolution of physical function (Bath Ankylosing Spondylitis Functional Index, BASFI) and its relationship with pain improvement.

- Evaluate patient relevant outcomes, including sleep, mental health, and health-related quality of life under routine care conditions.

- Describe the occurrence and evolution of peripheral manifestations (arthritis, dactylitis, and enthesitis) and extra-musculoskeletal manifestations (EMMs; acute anterior uveitis, inflammatory bowel disease, and psoriasis) over follow-up.

- Characterize patterns of treatment and persistence, reasons for discontinuation, and associations between persistence and early improvements in pain and other outcomes.

- Evaluate the safety profile of filgotinib including adverse drug reactions, adverse events of interest, special situations (including pregnancies), and deaths.

Exploratory

- Compare primary and secondary outcomes across clinically relevant subgroups (e.g., biological disease-modifying antirheumatic drug (bDMARD)/targeted synthetic disease-modifying antirheumatic drug (tsDMARD)-naïve vs bDMARD/tsDMARD-experienced; different countries or care settings).

- Identify baseline characteristics and early pain trajectories that predict sustained or improved pain response and treatment persistence.

- Explore profiles linking pain mechanisms, disease activity, and treatment persistence.

Study Design:
Prospective, multi-country, single-arm non-interventional study (NIS) with primary data collection from patients' medical records and routine clinical documentation. Treatment decisions remain entirely at the discretion of the treating physician according to routine practice and applicable product label. No study-specific diagnostic or therapeutic procedures outside routine clinical care will be mandated.

Patients initiating filgotinib as part of their routine clinical care will be documented at baseline (before filgotinib initiation), and at approximately 3 (±1), 6 (±2), 12 (±2), 18 (±2), and 24 (±2) months or until discontinuation of the study.

Baseline information may be collected within approximately 30 days prior to the first dose of filgotinib. Medical history, prior axSpA treatment, and concomitant diseases will be documented, as will current axSpA treatment and concomitant medication (with focus on pain medication), throughout the study.

Patients will enter diary data (9 questions including pain, fatigue, morning stiffness) using their own electronic devices daily in the first week, then weekly until week 4, then monthly until study end.

Setting and Study Population:

Setting: Approximately 50 rheumatology practices and clinics across Europe.

Inclusion criteria:

- Patients must meet one of the following indication-specific criteria:
  (a) Active non-radiographic axial spondyloarthritis, in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)
  OR
  (b) active ankylosing spondylitis (radiographic axial spondyloarthritis) in adult patients who have responded inadequately to conventional therapy.
- Independent treatment decision: The treating physician has decided to initiate filgotinib in accordance with the local product label and applicable reimbursement rules, independently of and prior to any consideration of the patient's participation in this study.
- Ability and willingness to provide patient-reported data: In the opinion of the investigator, the patient is able and willing to complete the required patient reported outcomes ePRO assessments using an electronic device (smartphone/tablet/computer), with reasonable support if needed (e.g., assistance by site staff or a caregiver), and to comply with planned visits and assessments.
- Written informed consent prior to any study-specific data collection.

Exclusion criteria:

- Current participation in an interventional clinical trial (e.g., randomized or blinded study, or a trial with protocol-mandated investigational procedures beyond routine care). Participation in other non-interventional studies or disease registries is permitted provided it does not interfere with the objectives, data quality, or conduct of the present study.
- Prior treatment with filgotinib (at any time prior to the index date/filgotinib initiation for this study).
- Concomitant treatment for axSpA with other approved advanced therapies (e.g. bDMARDs or tsDMARDs).

Variables:

- Demographic and baseline characteristics: Socio-demographics; body mass index; smoking status; axSpA history and phenotype; medical history; comorbidities.
- Treatment exposure: Prior and current axSpA treatments; filgotinib treatment (dose, regimen, modifications); concomitant medications.
- Clinical outcomes: Tender and swollen joint counts; dactylitis; enthesitis; extra-musculoskeletal manifestations; Physician Global Assessment; C-reactive protein.

- Patient-reported outcomes:
  - ePRO diary (spinal pain, nocturnal spinal pain, fatigue, sleep, activity limitation, rescue medication);
  - PRO questionnaires at visits (ASDAS, BASDAI, BASFI, Assessment of SpondyloArthritis international Society Health Index (ASAS-HI), Hospital Anxiety and Depression Scale (HADS), Patient Global Assessment, Patient Acceptable Symptom State, patient satisfaction);
  - Pain phenotyping: spinal pain (total and nocturnal); painDETECT; Widespread Pain Index (WPI).
- Safety:
  - Adverse drug reactions
  - Adverse events of interest:
    - Serious and opportunistic infections (including herpes zoster)
    - Major adverse cardiovascular events (MACE)
    - Venous thromboembolism (VTE)
    - Hyperlipidemia
    - Malignancies except NMSC
    - Non-melanoma skin cancer (NMSC)
    - Gastrointestinal (GI) perforation
    - Fractures
  - Special situations (including pregnancies).
  - Deaths.

Data Sources:

- Investigator-reported data: electronic case report form (eCRF).
- Electronic diary (with paper backup).
- PRO questionnaires around clinical visits: electronic, with paper-back-up transcribed into the eCRF.

Study Size:
Approximately 400 patients.

Data Analysis:
Analyses will be primarily descriptive. Continuous variables will be summarized using mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables will be summarized using counts and percentages. Where appropriate, descriptive estimates will be presented with 95% confidence intervals (CIs). Longitudinal outcomes will be described using repeated-measures summaries and trajectories. Time-to-event outcomes, such as treatment persistence, will be analysed using Kaplan-Meier methods, including estimates with 95% CIs where applicable. Subgroup analyses will be exploratory.

For the statistical analysis, analysis windows will be defined separately from data collection windows. Data collection will reflect routine clinical care and may occur at variable time points. For descriptive longitudinal analyses, documented routine-care visits will be assigned to prespecified, non-overlapping analysis windows around baseline and approximately 3, 6, 12, 18, and 24 months. The exact definition of these windows, including rules for assigning visits to windows and handling multiple or missing observations within a window, will be specified in the Statistical Analysis Plan (SAP). Detailed statistical methods will be specified in the Statistical Analysis Plan (SAP).
Milestones (approximately): Start of data collection: Q4 2026 Recruitment period: 18 months End of recruitment: Q2 2028 End of data collection: Q2 2030 Final Clinical Study Report: Q4 2030

5. AMENDMENT AND UPDATES

Protocol Version 2.0 Amendment 1 (21 October 2026):

Inclusion criteria in the Abstract and Section 9.2.1 were aligned with the axial spondyloarthritis indication wording in the product information. For nr-axSpA, objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), together with an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs), are now explicitly required; for r-axSpA, an inadequate response to conventional therapy is explicitly required.

Table 3 and footnote c were clarified to document these label-specific eligibility criteria from routine clinical care.

9.1.1. states that no study-specific CRP measurement or MRI is mandated.

No changes were made to the study objectives, endpoints, design, visit schedule, sample size, or safety reporting.

6. MILESTONES

Table 1. Milestones

Milestone	Planned Date
Start of Data Collection	Q4 2026
End of Data Collection	Q2 2030

Milestone	Planned Date
Clinical Study Report	Q4 2030
Study Progress Report	Every 6 months
Interim Report of Study Results	Not applicable
Registration in the HMA-EMA Catalogues of Real-world Data Sources and Studies	{DD Month YYYY}

7. RATIONALE AND BACKGROUND

7.1. Disease Background

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that primarily affects the sacroiliac joints (SIJ) and the spine [1]. The umbrella term axSpA comprises two subtypes distinguished by the presence or absence of definite structural damage in the SIJ on plain radiographs: radiographic axSpA (r-axSpA), historically termed ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA), respectively [2, 3].

R-axSpA is defined by definite radiographic sacroiliitis according to the modified New York criteria (at least bilateral grade II or unilateral grade III changes), whereas nr-axSpA includes patients who fulfil the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA but do not show definite sacroiliitis on conventional radiographs. In nr-axSpA, active inflammation may still be detectable by magnetic resonance imaging of the SIJ (particularly bone marrow edema/osteitis in typical subchondral locations), and the diagnosis is further supported by clinical features and biomarkers such as Human Leukocyte Antigen (HLA)-B27 positivity and elevated C-reactive protein (CRP). Importantly, nr-axSpA and r-axSpA share a similar overall clinical presentation and burden of disease, including extra-musculoskeletal manifestations (EMM) [4], and are managed according to the same overarching axSpA management recommendations (e.g., by Assessment of SpondyloArthritis international (ASAS) – European Alliance of Associations for Rheumatology (EULAR)) [5]. It has been suggested that nr-axSpA and r-axSpA represent an artificial split of a single disease entity along a clinical continuum, with nr-axSpA often reflecting an earlier disease stage before radiographic changes become evident [6]. However, it should be considered that some patients presenting with nr-axSpA may not progress to r-axSpA if diagnosis and treatment is provided early, or due to their individual patient profile.

The epidemiology of axSpA reveals that it typically manifests in individuals under the age of 45 years, with a peak onset in the third decade of life. Historically, it was considered a male-dominated condition, but recent studies indicate a more balanced sex distribution, especially in nr-axSpA. The prevalence of axSpA varies globally: In Europe, the prevalence ranges from approximately 0.32% to 0.70%, with higher percentages observed in populations with a higher prevalence of HLA-B27, such as Scandinavian countries [7].

The pathophysiology of axSpA involves a complex interplay of genetic, immunological, and environmental factors. The HLA-B27 gene is present in a majority of axSpA patients, suggesting a genetic predisposition [8]. The disease is characterized by inflammation at the entheses, where

tendons and ligaments attach to bone, leading to pain and stiffness. Over time, this inflammation can cause new bone formation and fusion of the affected joint(s), a condition known as ankylosis. The interleukin (IL)-23/IL-17 pathway has been identified as a critical component in the inflammatory process, with cytokines such as tumor necrosis factor (TNF)-alpha playing a significant role [9].

AxSpA is associated with significant pain and disability [10]. In the early stages of the disease, active inflammation is the primary driver of symptoms, including pain, stiffness, fatigue, and poor quality of sleep. Over time, chronic inflammation can lead to structural changes, such as new bone formation, which contribute to loss of spinal mobility and impaired physical function. Despite lack of structural damage to the SIJ and spine, patients with nr-axSpA have comparable disease burden (disease activity, pain, impairments of physical function and quality of life) to those with r-axSpA [4].

Many patients with axSpA experience not only the core axial symptoms but also peripheral manifestations, including peripheral arthritis, enthesitis, and, to a lesser extent, dactylitis. In addition, EMMs such as acute anterior uveitis (AAU), inflammatory bowel disease, and psoriasis are frequently observed and contribute to the overall disease burden and impaired quality of life (QoL) [11]. The presence of these diverse clinical features underscores the need for a comprehensive, patient-centered treatment approach that addresses all aspects of the disease as well as associated comorbidities [12].

7.2. Current Treatment Goals and Options for axSpA

The primary treatment goal of axSpA is to maximize health-related QoL by reducing symptom severity through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalization of function and social participation [5].

Current treatment options for axSpA aim to reduce inflammation, manage pain, and maintain mobility. Non-steroidal anti-inflammatory drugs (NSAIDs) are typically the first-line pharmacological treatment for relief of pain and stiffness, and are recommended jointly by ASAS and EULAR [5]. In patients with persistently high disease activity despite conventional NSAIDs treatment, targeted therapies should be considered. These include tumor necrosis factor (TNF) inhibitors , interleukin-(IL)17A inhibitors (IL-17Ai), and Janus kinase inhibitors (JAKi). In routine clinical practice, treatment is commonly initiated with a TNFi or an IL-17Ai. Treatment choice may also be influenced by the presence of EMMs and comorbidities; for example, monoclonal antibodies against TNF may be preferred in patients with recurrent uveitis or inflammatory bowel disease, whereas IL-17Ai may be preferred in patients with significant psoriasis.

Physical therapy and regular exercise are also crucial components of management, helping to preserve range of motion and improve overall function. In severe cases, surgical interventions may be necessary to correct bone deformities or relieve pain.

Despite available treatments, a substantial proportion of patients experience suboptimal responses to advanced therapies, which can ultimately lead to irreversible structural damage, further loss of spinal mobility, functional limitations, and substantial impact on daily living and overall QoL [1].

Following failure of a first biological disease-modifying antirheumatic drug (bDMARD) or targeted synthetic disease-modifying antirheumatic drug (tsDMARD), treatment adaptation is often required. In line with ASAS-EULAR recommendations, this may involve switching to another bDMARD or tsDMARD, either within the same therapeutic class or to a treatment with a different mechanism of action. Evidence to support the superiority of one treatment sequence over another remains limited, and both cycling and mechanism switching are part of current clinical practice [5, 13, 14]. Among the available treatment options, limitations of bDMARDs include the risk of immunogenicity, injection-site reactions, burdensome administration requirements, and delayed onset of action [15]. Among currently available JAKi, upadacitinib is approved for patients with r-axSpA and nr-axSpA, whereas tofacitinib is restricted to r-axSpA. A limitation of both approved JAKi is the absence of dosing flexibility, as both upadacitinib and tofacitinib are available only in fixed-dose regimens, leaving no possibility to tailor treatment based on individual characteristics, comorbidities, or response.

These challenges underscore the need for a broader range of therapeutic options that can address the full spectrum of axSpA and support individualized treatment strategies.

7.3. Rationale for Filgotinib Development in axSpA

JAKi, a group of tsDMARDs that block the intracellular JAK-signal transducer and activator of transcription (JAK-STAT) signaling pathway, represent treatment options for patients with axSpA who have an inadequate response (IR) to conventional therapy, including NSAIDs [16, 17].

JAK-STAT signaling is involved in the intracellular signaling of several cytokines relevant to the pathogenesis of axSpA, including JAK-dependent pathways such as IL-6, IL-7, IL-23, and interferon-γ [16, 17]. Although TNF-α and IL-17 are not directly inhibited by JAKi, JAK-dependent cytokine networks interact with broader inflammatory pathways, including the IL-23/IL-17 axis, and may contribute to chronic inflammation, pain, and structural damage [16, 17].

The oral administration of JAKi could offer a convenient alternative to injectable bDMARDs, which may improve patient adherence and patient-reported outcomes such as QoL [18]. Although safety considerations have been raised regarding the use of JAKi in certain higher-risk populations, including older patients (≥65 years) and those with a history of, or risk factors for, cardiovascular disease, malignancies, or venous thromboembolism (VTE), these risks should be interpreted in the context of the axSpA population that is generally younger and has fewer comorbidities compared with populations studied in other inflammatory diseases such as rheumatoid arthritis (RA) [19].

Filgotinib, a JAK1 preferential inhibitor, was first approved in the European Union (EU) on 24 September 2020 for the treatment of RA. Filgotinib is currently approved for the treatment of RA and for ulcerative colitis in more than 30 countries, including the EU, United Kingdom, Japan, Taiwan, South Korea, and Singapore. Filgotinib is available as a 100 mg or 200 mg film-coated tablet for oral use [20].

7.4. Filgotinib in the axSpA Clinical Development Program

The axSpA clinical development program consists of a completed supportive Phase 2 study (TORTUGA) in 116 patients with r-axSpA and the pivotal Phase 3 OLINGUITO program (up to Week 104) in 495 patients with active axSpA (including IR or those intolerant to NSAIDs and including bDMARD-naïve and bDMARD-experienced patients), and its open-label extension (OLE) over 130 weeks.

TORTUGA (GLPG0634-CL-223; EudraCT: 2016-003636-21) was a randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of filgotinib 200 mg q.d. for 12 weeks in patients with active r-axSpA (AS). Filgotinib 200 mg q.d. was efficacious and well tolerated in this patient population [21]. The results of TORTUGA were previously submitted as supportive safety data in the initial application for the RA indication. This study provided preliminary evidence of efficacy in r-axSpA of the filgotinib 200 mg dose and is also part of the integrated summary of safety for the new axSpA indication.

OLINGUITO (GLPG0634-CL-336; EUCT: 2022-5054-10-01) consists of 2 randomized, double-blind, placebo-controlled, multicenter, parallel-group studies under one Phase 3 protocol: Study A in 258 patients with r-axSpA and Study B in 237 patients with nr-axSpA [22]. Eligible patients in each study (A and B) were randomized in a 1:1 ratio to receive filgotinib 200 mg q.d. or placebo up to Week 16 in a double-blind treatment period (assessment of the primary endpoint; Assessment of SpondyloArthritis international Society 40% improvement [ASAS40] response), stratified by high-sensitivity CRP and prior use of bDMARD(s) (bDMARD-naïve or those with non-IR to prior bDMARD(s) versus bDMARD-IR). The double-blind treatment period was followed by an open-label treatment period, where patients aged <65 years and without pre-specified risk factors received filgotinib 200 mg q.d. up to Week 52, and a dose de-escalation period up to Week 104. After Week 16, patients aged ≥65 years and/or patients with pre-specified risk factors were to be treated with the lowest effective dose (100 mg or 200 mg q.d. based on their response) up to Week 104. After Week 104, patients who achieved ASAS40 response without high disease activity, per investigators' judgement, will enter the OLE period (in four countries). Overall, the study will provide long-term data on sustained efficacy and safety for up to 4 years among participants who remain on treatment and continue to derive clinical benefit.. As of June 2026, both the Phase 3 trial and the OLE remain ongoing.

7.5. Pain Mechanisms and Role of JAK Inhibition

Patients with axSpA consistently rank rapid and sustained relief of back pain, improvement in fatigue, sleep, morning stiffness, and physical function, and the ability to maintain work and social roles among their top treatment priorities [5, 23]. Pain in axSpA is multifactorial: nociceptive pain related to active inflammation and structural damage may coexist with neuropathic and nociplastic pain mechanisms [24, 25]. The latter pain components are associated with higher disease burden, worse patient-reported outcomes, and reduced work participation, and may respond less well to purely anti-inflammatory approaches [23, 24, 26].

Cytokines implicated in axSpA pathogenesis signal directly or indirectly through the Janus kinase/signal transducer and activator of transcription (JAK/STAT) cascade, a core pathway in the initiation and progression of spondyloarthropathies. Beyond its immunologic effects,

JAK/STAT signalling also contributes to nociception, and JAKi have been associated with rapid pain relief [16, 27].

7.6. Research Opportunities

While randomized clinical trials of filgotinib in axSpA – including the Phase 2 TORTUGA [28] and the Phase 3 OLINGUITO trials [22] – have demonstrated favorable effects on disease activity, imaging outcomes and a broad set of patient-reported endpoints, there is now an opportunity to generate complementary real-world evidence. In particular, prospective observational data can characterise patient-relevant symptom trajectories in routine clinical practice, including pain (and its inflammatory versus non-inflammatory components), fatigue, sleep, morning stiffness, mental health and health-related QoL, as well as disease activity control in patients treated with filgotinib.

Importantly, the very early phase of treatment (i.e., the first days and weeks after initiation) in inflammatory diseases is highly relevant from a patient perspective [29]: rapid improvements in pain, fatigue, stiffness, and sleep are key determinants of early treatment satisfaction and may directly influence adherence, persistence, and long-term treatment success. These early symptomatic dynamics, especially under everyday clinical practice conditions and across different pain mechanisms, have not yet been sufficiently characterised in filgotinib-treated axSpA populations.

Given the high burden of disease, the complexity of symptom mechanisms, and the central importance of patient-reported outcomes, there is a clear need for observational studies that build on the positive results observed in OLINGUITO, complement the randomized trials, and capture these dimensions in routine clinical practice.

8. RESEARCH QUESTIONS AND OBJECTIVES

This non-interventional, multi-country prospective cohort study is designed to evaluate the effectiveness and safety of newly initiated filgotinib in adult patients with r-axSpA and nr-axSpA in routine clinical practice. The study focuses on the early and sustained course of spinal pain, with particular attention to the characterization of pain components and trajectories at early time points after treatment initiation, as well as the evaluation of longer-term outcomes up to 24 months. Changes in pain will be interpreted in relation to parallel assessment of disease activity (ASDAS) and other routine axSpA outcomes. Treatment persistence and its relationship with patient-relevant improvements will also be characterized.

The study will assess both clinical and patient-relevant aspects of treatment effectiveness, including disease activity, physical function, mobility, pain, treatment persistence, and safety. By combining routine clinical data with multidimensional patient-reported outcomes, it will provide a comprehensive understanding of filgotinib effectiveness in axSpA and inform future clinical practice, guideline development, and health-technology assessments.

8.1. Primary Objective

The primary objective of the study is to:

- Assess the absolute change from baseline in total spinal pain following initiation of filgotinib, with a specific focus on early improvements up to Month 3 and sustained or further improvement up to Month 24.

8.2. Secondary Objectives

The secondary objectives of the study are to:

- Evaluate the effect of filgotinib on disease activity (Ankylosing Spondylitis Disease Activity Score, ASDAS), including change from baseline and responder status, and examine the relationship between changes in disease activity and changes in spinal pain.
- Evaluate the effect of filgotinib on nocturnal spinal pain and mechanistic pain features, assessed by change from baseline in nocturnal spinal pain and in painDETECT and Widespread Pain Index (WPI) scores, as well as by responder status (minimal clinically important improvement, MCII).
- Assess disease activity by evaluating changes in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) total and item-level scores and their association with spinal pain outcomes.
- Examine the evolution of physical function (Bath Ankylosing Spondylitis Functional Index, BASFI) and its relationship with pain improvement.
- Evaluate additional patient-relevant outcomes, including sleep, mental health, and health-related quality of life (QoL) under routine care conditions.
- Describe the occurrence and evolution of peripheral manifestations (arthritis, dactylitis, and enthesitis) and extra-musculoskeletal manifestations (EMMs; acute anterior uveitis (AAU), inflammatory bowel disease, and psoriasis) over follow-up.
- Characterize patterns of treatment and persistence, reasons for discontinuation, and associations between persistence and early improvements in pain and other outcomes.
- Evaluate the safety profile of filgotinib, including adverse drug reactions, adverse events of interest, special situations (including pregnancies), study discontinuations due to adverse events, deaths.

8.3. Exploratory Objectives

Exploratory objectives are to:

- Compare primary and secondary outcomes across clinically relevant subgroups (e.g., bDMARD/tsDMARD-naïve vs bDMARD/tsDMARD-experienced; different countries or care settings).
- Identify baseline characteristics and early pain trajectories that predict sustained pain response and treatment persistence.
- Explore profiles linking pain mechanisms, disease activity, and treatment persistence.

The primary, secondary and exploratory objectives aligned with endpoints are listed in Table 2.

Table 2. Objectives and Endpoints

Tier	Objective (domain)	Key endpoints	Timepoints
Primary			
	Pain: early total spinal pain benefit	Total spinal pain on NRS: absolute change from baseline	Month 3
		ePRO diary [a] including changes in spinal pain	Daily in Week 1, weekly in Weeks 2-4, monthly thereafter
Secondary			
	Disease activity	ASDAS: change from baseline; response	Months 3/6/12/18/24
	Pain response	Nocturnal spinal pain: change from baseline; responder status (MCII [b])	Month 3
		Total spinal pain: responder status (MCII [b])	
	Pain reduction sustainability	Maintenance of pain reduction	Months 6/12/18/24
	Non-inflammatory pain	painDETECT and WPI: change from baseline	Months 3/12
	Patient-reported disease activity components	BASDAI: change from baseline	Months 3/6/12/18/24
	Physical function	BASFI: change from baseline	Months 3/6/12/18/24
	Multidomain patient impact	Mental health (HADS); HRQoL (ASAS-HI); fatigue and sleep on NRS: change from baseline	Months 3/6/12/18/24

	(validated PROMs and patient diary)	Patient Acceptable Symptom State (PASS) [b]: change from baseline "no" to "yes"	
	Clinical manifestations	TJC44/SJC44; dactylitis count; enthesitis; and peripheral arthritis: change from baseline EMMs (acute anterior uveitis, IBD, and psoriasis): presence	Months 3/6/12/18/24
	Treatment patterns, persistence of study drug, and concomitant medications	Time on filgotinib	Summaries at Months 3/6/12/18/24
	Safety	Incidence of adverse drug reactions; adverse events of interest; special situations (including pregnancies); study discontinuation due to adverse events; deaths	Continuous
Exploratory			
	Subgroups	Primary and secondary endpoints by subgroup [c]	Month 3 (primary); Months 12/24 supportive

[a] The ePRO diary comprises 9 brief items; the item list, collection schedule, and sources are provided in Section 9.4.1.6

[b] Responder defined as achieving the minimum clinically important improvement (MCII) concept as described by Tubach et al. [30] and specified in Section 9.7.7.

[c] Exploratory subgroup analyses may include r-axSpA versus nr-axSpA, bDMARD/tsDMARD-naïve versus experienced patients, presence versus absence of baseline EMMs, and other clinically relevant phenotypic subgroups. Subgroup definitions will be based on information documented in routine clinical care and specified in the SAP.

Abbreviations: ASAS-HI, Assessment of SpondyloArthritis international Society Health Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; EMMs, extra-musculoskeletal manifestations; ePRO, electronic patient-reported outcome; HADS, Hospital Anxiety and Depression Scale; IBD, inflammatory bowel disease; MCII, minimum clinically important improvement; NRS, numerical rating scale; PASS, Patient Acceptable Symptom State; PROM, patient-reported outcome measure; SJC, swollen joint count; TJC, tender joint count; WPI, widespread pain index.

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Regulatory Classification as Non-Interventional Study

This study is a non-interventional study (NIS) based on established regulatory criteria: the medicinal product is prescribed in the usual manner in accordance with the product label, local clinical practice, and reimbursement rules; the assignment of the patient to a particular therapeutic strategy is not decided in advance by the protocol but falls within current practice; the prescription decision is clearly separated from the decision to include the patient in the study; and no additional diagnostic or monitoring procedures are applied [31]. Accordingly, treatment decisions are made independently of study participation, and study-specific data collection is limited to observational documentation and patient-reported questionnaires.

Eligibility is defined in Section 9.2.1. Any CRP or MRI evidence used to establish nr-axSpA eligibility must originate from routine clinical care and is not mandated by the protocol.

This prospective, multi-country, observational single-arm cohort study is conducted in adult patients with axSpA who initiate filgotinib as part of routine clinical practice. Approximately 400 patients will be enrolled at about 50 sites (predominantly office-based rheumatology practices, complemented by selected hospital-based centers) in six European countries (Germany, Austria, the United Kingdom, Ireland, the Netherlands, and Belgium). Patients are expected to be enrolled over an estimated 18-month enrollment period and followed for 24 months after filgotinib initiation, or until filgotinib discontinuation or withdrawal from the study, whichever occurs first.

Treatment decisions, including the decision to initiate filgotinib, dosing and dose adjustments, concomitant medication use, switching, treatment cycling, and treatment discontinuation, are made entirely at the discretion of the treating physician, in accordance with the applicable local Summary of Product Characteristics (SmPC), applicable reimbursement rules, and standard of care.

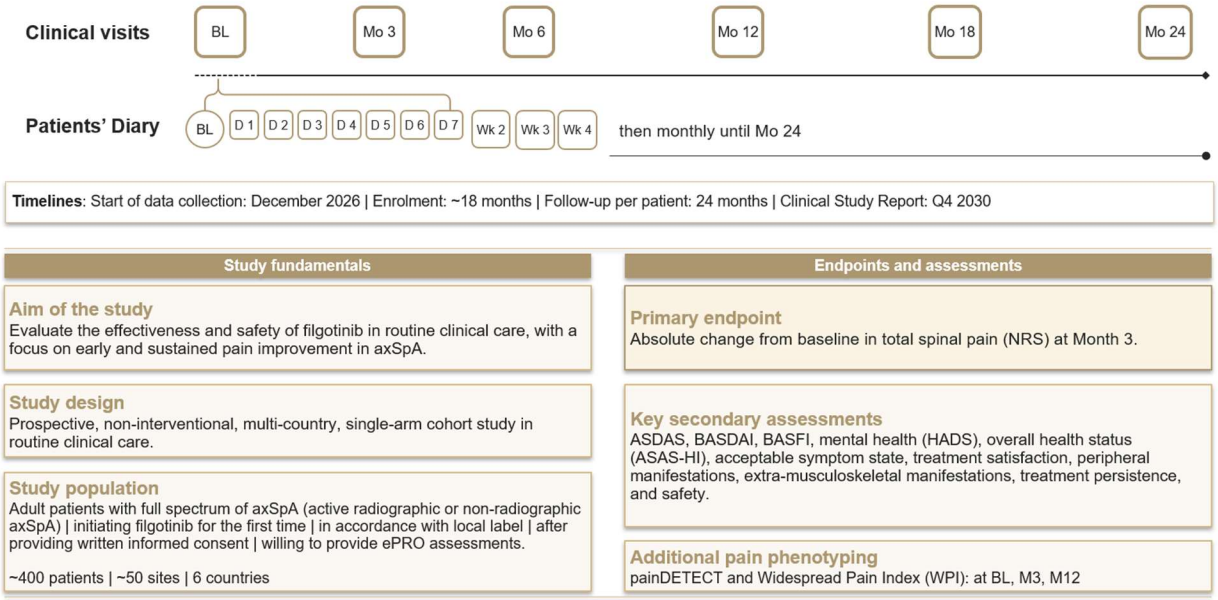
The study is purely observational and does not impose any additional diagnostic or therapeutic interventions beyond those performed as part of routine clinical practice. PRO measures are used to support and standardize the clinical assessment of symptoms and treatment benefit from the patient perspective under routine clinical practice conditions, without mandating any additional diagnostic or therapeutic interventions.

Participation in national or international registries and other non-interventional studies is permitted, provided that the respective assessments do not conflict with those in this study.

Baseline assessments may be collected within up to 30 days prior to filgotinib initiation or on the day of first intake of filgotinib, provided that the decision to start filgotinib was made independently of and prior to any discussion of study participation.

Physician assessments will be aligned with routine rheumatology visits around Months 3(±1), 6(±2), 12(±2), 18(±2), and 24(±2) or at filgotinib discontinuation/early study termination, with pre-defined visit windows, as summarized in the Schedule of Assessments (Table 3; Figure 1).

Figure 1. Study Flow



Abbreviations: ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BL, baseline; D, day; EDC, electronic data capture; eCRF, electronic case report form; Mo, month(s); NIS, non-interventional study; nr-axSpA, non-radiographic axial spondyloarthritis; PRO, patient-reported outcome; r-axSpA, radiographic axial spondyloarthritis; WPI, Widespread Pain Index; axSpA, axial spondyloarthritis

9.2. Setting and Study Population

9.2.1. Inclusion Criteria

1. Patients must meet one of the following indication-specific criteria:
   a) active non-radiographic axial spondyloarthritis, in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)
   OR
   b) active ankylosing spondylitis (radiographic axial spondyloarthritis) in adult patients who have responded inadequately to conventional therapy.

2. Independent treatment decision: The treating physician has decided to initiate filgotinib in accordance with the local product label and applicable reimbursement rules, independently of and prior to any consideration of the patient's participation in this study.

3. Ability and willingness to provide patient-reported data: In the opinion of the investigator, the patient is able and willing to complete the required ePRO assessments using an

electronic device (smartphone/tablet/computer), with reasonable support if needed (e.g., assistance by site staff or a caregiver), and to comply with planned visits and assessments.

4. Written informed consent prior to any study-specific data collection.

9.2.2. Exclusion Criteria

Patients will be excluded if any of the following apply:

1. Current participation in an interventional clinical trial (e.g., randomized or blinded study, or a trial with protocol-mandated investigational procedures beyond routine care). Participation in other non-interventional studies or disease registries is permitted provided it does not interfere with the objectives, data quality, or conduct of the present study.

2. Prior treatment with filgotinib (at any time prior to the index date/filgotinib initiation for this study).

3. Concomitant treatment for axSpA with other approved advanced therapies (e.g. bDMARDs or tsDMARDs.

9.2.3. Patient Classification

Patients will be classified for descriptive analyses and pre-specified exploratory subgroup analyses (including effectiveness, PROs, and treatment persistence) according to:

- r-axSpA vs nr-axSpA, based on imaging and clinical information in routine clinical care;
- bDMARD/tsDMARD-naïve vs bDMARD/tsDMARD-experienced (including prior JAKi exposure);
- presence vs absence of EMMs at baseline (e.g., history of inflammatory bowel disease, AAU, psoriasis); and
- other clinically relevant phenotypic subgroups.

9.3. Variables

Study variables will be collected prospectively from routine clinical practice using the eCRF and patient self-reported data using ePRO, as specified in the schedule of assessments (Table 3).

A detailed list of collected data fields, coding conventions and derivations will be provided in the eCRF completion guidelines and the SAP.

Table 3. Data Items and Timing of Documentation

Data to be provided if available or applicable	Clinical visit at baseline [a]	Patient diary d1-d7, weekly w2-w4, then monthly	Clinical visits at mo 3(±1), 6(±2), 12(±2), 18(±2), 24(±2)	Filgotinib discontinuation [b] or early study termination
Administrative and baseline characteristics				
Informed consent	X			
Socio-demographic characteristics (including age, sex, ethnicity, current employment status)	X			
Height, weight, and body mass index	X			
Smoking status (including e-cigarettes)	X			
axSpA history, phenotype, and indication-specific eligibility [c]	X			
Medical history	X			
Comorbidities	X			
Prior axSpA treatments [d]	X			
Current management				
Filgotinib axSpA treatment [e]	X		X	X
Concomitant medications [f]	X		X	X
Clinical assessment and laboratory (routine care)				
Tender and swollen joint counts	X		X	X
Dactylitis count	X		X	X
Enthesitis	X		X	X
EMMs (history at baseline; new/worsening events during follow-up)	X		X	X
Physician Global Assessment (PhGA)	X		X	X
CRP	X		X	X
Patient-reported outcomes (PRO)				
Diary (9 questions), completed electronically by the patient using their own device [g]	X	X	X	X

Data to be provided if available or applicable	Clinical visit at baseline [a]	Patient diary d1-d7, weekly w2-w4, then monthly	Clinical visits at mo 3(±1), 6(±2), 12(±2), 18(±2), 24(±2)	Filgotinib discontinuation [b] or early study termination
ePRO questionnaires [h] ASDAS BASDAI BASFI ASAS-HI HADS Patient Global Assessment (PtGA) Patient Acceptable Symptom State Patient satisfaction	X		X	X
Pain phenotyping questionnaires completed electronically [h] painDETECT Widespread Pain Index (WPI)	X		mo 3 and 12	X
Safety ADRs; AEIs [i]; special situations (including pregnancies); death	Safety events are recorded throughout study independent of clinical visits			

ADR, adverse drug reaction; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; d, day(s); eCRF, electronic case report form; EDC, electronic data capture; ePRO, electronic patient-reported outcome; EMM, extra-musculoskeletal manifestation; HADS, hospital anxiety and depression score; mo, month(s); PtGA, Patient Global Assessment; PhGA, Physician Global Assessment.

Day 1 = filgotinib initiation

a Baseline assessments may be collected within approximately 30 days prior to initiation, provided the decision to initiate filgotinib was taken independently of and prior to study participation.

b Patients discontinuing filgotinib may remain in the study and will be followed until Month 24 or early study termination (e.g., withdrawal of consent, loss to follow-up or death), in accordance with routine care and local feasibility.

c Includes axSpA symptom duration, disease duration, diagnosis date, r-axSpA vs nr-axSpA, HLA-B27 status, and family history and documentation of the applicable label-specific eligibility criteria: for nr-axSpA, objective signs of inflammation as indicated by elevated CRP and/or MRI and inadequate response to NSAIDs; for r-axSpA, inadequate response to conventional therapy. These data are documented from routine clinical care; no study-specific CRP testing, MRI, or treatment trial is mandated.

d Prior axSpA treatments: include drug name/class, dose/regimen (where available), start/end dates (where available), and reason for discontinuation; the most recent therapy prior to filgotinib initiation will be documented.

e Filgotinib treatment: include start date and starting dose, regimen (monotherapy vs combination), dose changes and reasons for dose change, and stop date. In case of changes between visits, information should be entered into the Medication eCRF without delay.

f For other axSpA medications: name and dose/regimen; start/end dates. For other (non ax-SpA) medications: name and start/end dates.

g The patient diary is preferably completed by patients using their own electronic devices. In exceptional cases, paper diaries may be used and transcribed by site staff. The 9-item diary refers to the preceding 24 hours and is to be completed daily in Week 1, weekly in Weeks 2 to 4, and monthly thereafter.

h The full PRO battery is to be filled out by patients electronically on their own device around routine clinical visits. Duration to fill out is about 30 minutes per clinical visit. As back-up, paper forms are available, which are transferred into the online CRF by site staff.

i Important identified/potential risks as defined in the current Risk Management Plan (Version 7, Feb 2024) include teratogenicity, major adverse cardiovascular events (MACE), hyperlipidemia, herpes zoster, varicella zoster, malignancies, non-melanoma skin cancer (NMSC), venous thromboembolism (VTE), serious and opportunistic infections, GI perforation, and fractures.

9.4. Data Sources

Data will be collected from clinical sites participating within Europe. Each investigator at the participating sites will offer the study to potentially eligible patients, for whom the independent decision to prescribe filgotinib has been made prior to inclusion into the study.

Baseline assessments may be collected within approximately 30 days prior to the first dose of filgotinib until the first dose. Prior axSpA treatment will be captured from the day of axSpA diagnosis.

Patients will not have to attend any additional visits or undergo any procedures outside of the standard of care (exception: questionnaires on patient-reported outcomes).

This study collects data via:

- Electronic case report forms (eCRF) completed by site staff, based on routine clinical records, physician assessments, and paper-based patient questionnaires.
- Electronic diary and ePRO entered by patients into the eCRF using their own devices. Patients will be instructed to enter ePRO data directly into the designated online system using their own electronic device (smartphone, tablet, or computer). If electronic entry is not feasible, paper diaries may be used. In such cases, site staff will transcribe the data into the eCRF/ePRO system in accordance with the data management procedures.

Where relevant, data may be complemented by review of electronic or paper medical records for baseline disease history, comorbidities, laboratory parameters, and concomitant medications.

There will be no automated or semi-automated transfer of data from clinical or laboratory information systems into the eCRF.

9.4.1. Patient-reported Outcomes

9.4.1.1. Pain

9.4.1.1.1. Total Spinal Pain and Nocturnal Spinal Pain

Spinal pain, a core symptom of axSpA, will be captured using an 11-point numeric rating scale (NRS; 0–10), where 0 represents "no pain" and 10 represents "pain as bad as you can imagine". Pain NRS measures are widely used in axSpA clinical trials and observational studies and are embedded in established axSpA disease activity constructs, thereby supporting the primary objective of quantifying early changes in spinal pain under real-world conditions.

Spinal pain will be assessed as:

- total spinal pain (NRS 0–10), and
- nocturnal spinal pain (NRS 0–10).

9.4.1.1.2. painDETECT

Neuropathic-like pain features are increasingly recognized as relevant contributors to pain burden and heterogeneity of response in axSpA. The painDETECT questionnaire is included to characterize neuropathic pain components and to support analyses of pain phenotypes [32].

painDETECT is a self-administered questionnaire consisting of sensory descriptor items, a pain pattern item, and a radiating pain item. The total score ranges from -1 to 38, with higher scores indicating a higher likelihood of neuropathic-like pain features. Commonly used interpretive categories are: ≤12 (neuropathic component unlikely), 13-18 (possible), and ≥19 (likely).

In this study, painDETECT will be documented at baseline and at the Month 3 and 12 visits to characterize neuropathic-like pain features at the primary efficacy timepoint (Month 3) and the maintenance phase (Months 12), enabling interpretation of pain trajectory patterns beyond the primary endpoint.

9.4.1.1.3. Widespread Pain Index (WPI)

Widespread pain features reflecting centrally mediated/nociplastic pain mechanisms are increasingly recognized in axSpA and may contribute to symptom burden and heterogeneity of treatment response. The Widespread Pain Index (WPI) is included to characterize the extent and distribution of pain beyond the spine as a pragmatic marker of widespread musculoskeletal pain.

The WPI is a count of painful body regions (0–19) experienced by the patient over the preceding week, as defined in the American College of Rheumatology (ACR) 2010 fibromyalgia criteria framework [33]. Higher WPI scores indicate more widespread pain and may be associated with higher symptom burden and functional impairment.

In this study, the WPI will be documented at baseline and at the Month 3 and 12 visits to describe the burden of widespread pain at the primary efficacy timepoint (Month 3) and in the

maintenance phase (Month 12). Together with painDETECT, the WPI will enable a multidimensional characterization of pain – from localized inflammatory spinal pain to broader widespread pain features – which supports the study objective of understanding pain trajectories and their relationship with functioning, sleep, fatigue, mental health, and work participation in routine axSpA care.

9.4.1.2. Disease Activity, Function and Global Assessment

9.4.1.2.1. Axial Spondyloarthritis Disease Activity Score (ASDAS)

The Axial Spondyloarthritis Disease Activity Score (ASDAS) is a composite measure of axSpA disease activity, integrating patient-reported symptoms with an objective marker of inflammation [34]. ASDAS is calculated using a validated formula based on back pain, duration of morning stiffness, peripheral pain/swelling, patient global assessment - and C-reactive protein (CRP), if available. Higher ASDAS values indicate higher disease activity.

Disease activity scores are commonly categorized as inactive disease (<1.3), low disease activity (≥1.3 to <2.1), high disease activity (≥2.1 to ≤3.5), and very high disease activity (>3.5); thresholds for improvement (clinically important improvement $\Delta \geq 1.1$ and major improvement $\Delta \geq 2.0$) are established and endorsed by ASAS/EULAR, and will be used for responder summaries as prespecified in the SAP [35].

9.4.1.2.2. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

As another instrument to assess disease activity, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a validated and widely used questionnaire that consists of 6 questions pertaining to the 5 major symptoms of axSpA: fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness, and duration of morning stiffness [36]. Each question will be rated using a numerical rating scale from 0 (none) to 10 (very severe). The BASDAI score is calculated by computing the mean of questions 5 and 6 and adding it to the sum of questions 1 to 4. This score is then divided by 5. The BASDAI change from baseline and 50% improvement response will be calculated.

9.4.1.2.3. Bath Ankylosing Spondylitis Functional Index (BASFI)

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a validated instrument designed to determine the degree of functional limitation in patients with axSpA [37, 38]. It consists of 10 questions, the first 8 addressing activities related to functional anatomy and the final 2 questions assessing the patients' ability to cope with everyday life. Each item is scored on a 0-10 numerical rating scale, with 0 indicating "easy" and 10 "impossible." The BASFI total is calculated as the mean of the 10 items, with higher scores indicating greater functional impairment.

9.4.1.2.4. Patient Global Assessment (PtGA)

Patient Global Assessment (PtGA) will be used as a patient-reported measure of overall disease burden in axSpA [39]. PtGA will be recorded on an 11-point numeric rating scale ranging from 0 ("not active at all") to 10 ("extremely active"). It will be collected at baseline and at routine

follow-up visits. In this study, PtGA will be summarized descriptively over time and analysed as change from baseline. PtGA also provides an important patient-centred measure for the interpretation of pain, function, and overall symptom burden.

9.4.1.3. Anxiety and Depression

9.4.1.3.1. Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) will be used to assess symptoms of depression and anxiety in participants of the axSpA study. It is a self-administered questionnaire comprising 14 items, divided into two 7-item subscales measuring anxiety (HADS-A) and depression (HADS-D), each rated on a 4-point Likert scale (0–3) with subscale scores ranging from 0 to 21, where higher scores indicate greater symptom severity [40]. The HADS is a widely used and validated instrument in patients with chronic physical conditions and has demonstrated good internal consistency and construct validity as a screening tool for psychological distress in clinical populations, making it appropriate for capturing the mental health burden in individuals with axSpA within this protocol.

9.4.1.4. Overall Health and Patient Acceptability

9.4.1.4.1. ASAS Health Index (ASAS-HI)

The ASAS Health Index (ASAS-HI) is an axSpA-specific patient-reported outcome developed by the Assessment of SpondyloArthritis International Society (ASAS) to capture overall functioning and health. It provides a broader patient-centered view of disease impact than symptom-only measures [41, 42].

ASAS-HI comprises 17 dichotomous items (“I agree”/“I do not agree”) covering domains such as pain, mobility, sleep, emotional function, energy, and participation in daily and social activities. Responses are summed to a total score from 0 to 17, with lower scores indicating better health/functioning (less disease impact). Cutoffs are ≤5 (good), >5 – <12 (moderate), and ≥12 (poor health). The simple response format supports feasibility in routine care and observational research.

In this study, ASAS-HI will be used as the core axSpA-specific health/functional status measure to describe how improvements in spinal pain and disease activity translate into broader everyday functioning and participation over time. ASAS-HI complements BASFI: while BASFI focuses mainly on physical function, ASAS-HI additionally captures wider health domains (e.g., sleep, emotional impact, and participation), thereby reducing the risk of missing meaningful patient benefit beyond physical disability. ASAS-HI will be administered at Baseline and at the clinical follow-up visits.

9.4.1.4.2. Patient Acceptable Symptom State (PASS)

The Patient Acceptable Symptom State (PASS) is a patient-reported outcome concept reflecting whether patients consider their current symptom state acceptable. In axSpA, PASS dichotomously captures patient-perceived acceptability of the current disease state (yes/no) and

therefore provides a clinically meaningful patient-centered outcome beyond continuous scores [43].

PASS will be assessed at baseline and clinical follow-up visits using the question: “Considering all the different ways your disease is affecting you, if you would stay in this state for the next months, do you consider that your current state is satisfactory?"[44].

9.4.1.5. Treatment Satisfaction

Treatment satisfaction will be assessed as a patient-reported outcome reflecting the patient’s overall subjective evaluation of filgotinib treatment in routine clinical practice. In line with the methodology applied in the German RABBIT-RA registry [45], treatment satisfaction will be captured using two separate single-item questions, addressing:

- treatment effectiveness, and
- treatment tolerability.

For each item, patients will rate their satisfaction using a four-category scale (very satisfied, rather satisfied, somewhat dissatisfied, very dissatisfied).

Treatment satisfaction outcomes will be analysed descriptively over time and interpreted in conjunction with clinical effectiveness measures, patient-reported symptom burden, treatment persistence, and safety outcomes.

9.4.1.6. Patient Diary

Patients will be requested to complete a short set of remote assessments on various aspects of their health (electronic diary, on patients’ own device). It is intentionally brief to support adherence with the assessment. The diary will comprise 9 items:

1. Total spinal pain due to axSpA (NRS 0–10; past 24 hours)
2. Nocturnal spinal pain (NRS 0–10; last night/past 24 hours)
3. Morning stiffness severity (NRS 0–10; today)
4. Morning stiffness duration (minutes; today)
5. Fatigue (NRS 0–10; today)
6. Sleep quality (NRS 0–10; last night)
7. Number of awakenings (integer; last night)
8. Activity limitation due to axSpA (NRS 0–10; today)
9. Rescue analgesic/NSAID taken in past 24 hours? (Yes/No)

No instruments with a recall period longer than 1 day (e.g., “past 7 days”, “past 2 weeks”, “past 4 weeks”) will be included in the daily diary (in contrast to other PRO instruments like BASDAI).

The diary is to be filled daily during the first week, then weekly until week 4, and then monthly until study end (independent of clinical visits).

9.4.2. Physician-reported Outcomes

9.4.2.1. Swollen and Tender Joint Counts

Swollen and tender joint counts will be assessed using the standard 44-joint format (TJC44 and SJC44) to capture the extent and course of peripheral joint involvement as judged by the physician. At each on-site visit, investigators will examine the predefined set of 44 peripheral joints and record, for each joint, whether it is clinically tender (TJC44) and/or swollen (SJC44). The results will be entered as numerical totals, with higher TJC44 and SJC44 values indicating a greater burden of peripheral arthritis. The same 44-joint assessment will be applied consistently for each patient across all visits to allow meaningful longitudinal comparisons.

9.4.2.2. Dactylitis Count

Dactylitis, where present, will be documented by the physician using a dactylitis count, defined as the number of digits with diffuse swelling compatible with dactylitis that are tender on palpation [46, 47].

9.4.2.3. Enthesitis

Enthesitis will be assessed at each visit as present or not present. If scores of the Leeds Enthesitis Index (LEI) or Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) are available in patient files, they will be recorded.

9.4.2.4. Extra-Musculoskeletal Manifestations

Patients will be assessed at each visit if they have experienced a new onset of inflammatory bowel disease, psoriasis or AAU, or a flare hereof (for subject with pre-existing EMM) since the last visit.

9.4.2.5. Physician Global Assessment

Physician Global Assessment (PhGA) will be used as a pragmatic, single-item measure of the physician's overall impression of the patient's disease activity. It is recorded as an integer on a numeric 11-point scale, where 0 indicates no disease activity and 10 indicates severe disease activity. This approach serves to integrate clinical findings, patient history, and relevant laboratory or imaging results into one global score. The PhGA is widely used across rheumatologic conditions as an outcome in clinical trials and routine care, and provides a simple, reproducible summary of disease status that can be analysed longitudinally alongside patient-reported and biomarker outcomes in this study.

9.4.3. C-reactive Protein

C-reactive protein (CRP) will be recorded as a key laboratory marker of systemic inflammation and as an essential component of ASDAS. In routine clinical practice, CRP will be measured by local laboratories according to standard methods and recorded in mg/L together with the sampling date. Samples for measurement of CRP should be taken outside clinical infections (e.g., common cold).

For ASDAS calculation, the CRP value closest to the clinical assessment date within the predefined visit window will be used [48].

9.4.4. axSpA Medications and Co-Medications

Treatment of axSpA in this NIS reflects routine clinical practice and is fully at the discretion of the treating physician, in accordance with the local SmPC, applicable reimbursement rules, and current recommendations (e.g., ASAS–EULAR). No study-mandated treatment decisions or restrictions are imposed.

9.4.4.1. axSpA Medications

All pharmacological treatments for axSpA during the study will be documented to describe treatment patterns, contextualize effectiveness outcomes, and support analyses of persistence and switching.

axSpA medications include:

- Filgotinib (index treatment):
  Including starting dose, regimen, dose adjustments, temporary interruptions, and stop, with dates and reasons for discontinuation where available.

- Conventional synthetic DMARDs (csDMARDs):
  Primarily used for peripheral manifestations where applicable (e.g., methotrexate, sulfasalazine, or leflunomide).

- bDMARDs:
  Prior use, including tumor necrosis factor inhibitors (TNFi) and interleukin-17 inhibitors (IL-17i) will be recorded.

- NSAIDs:
  Continuous or on-demand use, including drug name, dose/regimen, and changes over time.

- Systemic glucocorticoids:
  Use, dose, route of administration, and duration where prescribed in routine care.

For all axSpA-directed medications, the following information will be captured in the eCRF where available: drug name/class, dose and regimen, start date, end date (or ongoing status), dose changes over time, and reason for initiation, modification, or discontinuation.

9.4.4.2. Concomitant Medications including Analgesics

Concomitant medications prescribed for comorbid conditions (e.g., cardiovascular disease, gastrointestinal disease, psychiatric conditions, osteoporosis) will be recorded to characterize the study population and support safety analyses. For these medications, drug name, dose, and start/end dates (where available) will be documented.

In the same CRF section, analgesic and pain-relieving medications will be recorded, including non-opioid analgesics (e.g., paracetamol), opioids, adjuvant or centrally acting pain medications used for pain modulation (e.g., gabapentin or selected antidepressants), and other centrally acting pain medications.

The use of rescue pain medication will also be recorded in the patient diary (see Section 4.9.1.6).

9.4.4.3. Treatment Modifications and Persistence

Treatment modifications during follow-up — including dose changes, temporary interruptions, switching to another advanced therapy, or permanent discontinuation — will be documented together with the corresponding dates and reasons (e.g., lack of effectiveness, adverse events, patient preference).

For documentation purposes, a temporary treatment interruption is defined as a documented pause in an ongoing therapy with the intention to restart the same treatment or with subsequent documented re-initiation of the same treatment. Prolonged treatment gaps without documented intention to restart will be considered treatment discontinuations for treatment-pattern and persistence analyses; detailed operational cut-offs and analysis rules will be specified in the SAP.

9.4.4.4. Filgotinib Discontinuation and Re-Initiation

In case of filgotinib discontinuation, the date of discontinuation, the anticipated permanence of discontinuation (e.g., temporary or permanent) and the date of treatment reinitiation (where relevant), reasons for discontinuation (e.g., patient's decision, investigator's decision, lack of effectiveness, primary non-response, secondary loss of response, adverse reaction, reimbursement reasons, health insurance reasons, medication economic burden, noncompliance or other reasons) and information of the patient's subsequent axSpA treatment will be collected.

The patient will remain in the study and will be followed up until reaching the defined end of the study (i.e., 24 months after enrolment) or until documented premature end (e.g., due to lost to follow-up, withdrawal of consent, or death). Any subsequent changes in patient's therapy will be recorded until the patient completes the study.

9.5. Study Size

This study is primarily descriptive and aims to estimate the mean within-patient change from baseline to Month 3 in the primary endpoint: absolute change of total spinal pain.

The planned sample size is approximately 400 patients, driven by feasibility across participating sites and by the need to obtain precise estimates of changes in pain under routine clinical practice, including descriptive subgroup summaries.

Assuming that approximately 20% of patients may have missing Month-3 pain assessments, about 320 patients are expected to contribute to the Month-3 analysis. Under plausible assumptions for the variability of within-patient change (standard deviation 2.0-3.0 NRS points),

the expected 95% confidence interval (CI) half-width for the mean change at Month 3 is approximately:

- SD 2.0 → half-width ≈ ±0.22 NRS points
- SD 2.5 → half-width ≈ ±0.27 NRS points
- SD 3.0 → half-width ≈ ±0.33 NRS points

This level of precision is considered sufficient for clinically interpretable estimation of mean changes in total spinal pain.

The sample size also supports meaningful descriptive subgroup analyses (e.g., r-axSpA vs nr-axSpA; bDMARD/tsDMARD-naïve vs bDMARD/tsDMARD-experienced; baseline pain severity categories). For a subgroup size of n≈ 100 evaluable patients, the expected 95% CI half-width for the mean change is approximately ±0.49 NRS points assuming SD 2.5 (and ±0.59 assuming SD 3.0). For smaller subgroups (e.g., n ≈ 50 evaluable patients), the corresponding half-width is approximately ±0.69 assuming SD 2.5.

Subgroup results will be interpreted descriptively.

9.6. Data Management

9.6.1. EDC System

eCRFs will be built in an EDC system to collect the data listed in the variables section. Personal identifying data such as names, exact birth dates, health record, or social security identifiers will not be collected.

Investigational site users will receive a unique username and password per user generated from the EDC system following completion of the EDC system training. Completion of training and receipt of username/password will allow users to enter data into the EDC system. Investigators will electronically sign the eCRF to confirm responsibility for data following completion of data entry and data quality activities. Study datasets will be stored on secure network drives of the sponsor with access restricted to authorized personnel only.

Clinical outcome assessment (COA) data, including ePRO diary data, electronic or paper-based PRO questionnaires, physician-reported assessments and derived scores, will be managed according to predefined data management procedures.

Patient diary data and ePRO will be collected in a separate patient-facing EDC system, using individual registration codes provided by the site. Personal login data required for the EDC access, such as the patient's e-mail address, will be stored separately from the questionnaire responses and protected by appropriate technical safeguards. Data transmission will occur via secure connections. Diary and ePRO entries will be attributable to the registered patient and date- and time-stamped.

Paper diaries may be used as a backup where electronic entry is not feasible; in such cases, trained site staff will transcribe the data into the electronic system according to predefined procedures. Data from the patient-facing ePRO system and the site-based EDC will be linked for analysis using predefined study identifiers. Derived COA variables and scores will be calculated

according to predefined scoring algorithms and described in the SAP and/or data management plan.

9.6.2. Medical Coding and Dictionaries

To support consistent analysis and reporting, relevant verbatim terms will be coded using standardized medical dictionaries, where applicable. Medical history and concomitant diseases will be coded using ICD-10. Clinical events, including adverse events, adverse drug reactions, special situations, and other relevant safety outcomes, will be coded using MedDRA. Prior and concomitant medications will be coded using the WHO Anatomical Therapeutic Chemical (ATC) classification system; where required, medication names will be mapped to the corresponding active substance and ATC code. The original verbatim terms as reported by the site will be retained in the database together with the coded term, code, dictionary, and dictionary version used. Coding will be performed centrally according to predefined coding conventions. Ambiguous or insufficiently specific terms may be queried or medically reviewed before final coding. The applicable dictionary versions and detailed coding rules, including the handling of uncodable or ambiguous entries, will be described in the data management plan and/or SAP.

9.7. Data Analysis

This NIS is primarily descriptive and exploratory. No formal hypothesis testing is pursued. Inferential methods may be applied to support interpretation.

9.7.1. Estimands and Intercurrent Events

For the two principal pain endpoints (total spinal pain and nocturnal spinal pain) and secondary effectiveness endpoints, the primary estimand is the mean within-patient change from baseline to Month 3 under a treatment-policy strategy, i.e., irrespective of intercurrent events occurring between baseline and Month 3. Intercurrent events of interest include, but are not limited to, treatment discontinuation, treatment switching, temporary interruption, dose changes, initiation/escalation of concomitant pain therapies (e.g., analgesics, NSAIDs, corticosteroids), and study withdrawal/loss to follow-up.

Observed data will be used for primary analysis. The handling of missing Month-3 assessments (e.g., due to missed routine visits or study withdrawal) and sensitivity analyses using alternative strategies (e.g., hypothetical strategy via multiple imputation; composite strategy where appropriate) will be pre-specified in the SAP.

9.7.2. Analysis Populations, General Principles, and Descriptive Methods

Patient enrollment: A summary of patient enrollment will be provided, presenting the number and percentage of patients enrolled. For each column, the denominator for the percentage calculation will be the total number of patients analyzed for that column.

In general, for continuous variables, descriptive summary statistics will be provided including number of patients (N), mean, standard deviation (SD), minimum, median, and maximum, together with the number of missing values. Categorical variables will be summarized with numbers and percentages, with missing values as separate category. Incidence rates and 95% CIs will be provided where applicable (e.g., for safety events). Demographics and baseline

characteristics will be summarized using descriptive statistics. Analysis windows will be defined in the SAP.

Unless otherwise specified, endpoints are evaluated as change from baseline to the respective follow-up timepoint; for the two principal pain endpoints at Month 3, this corresponds to the treatment-policy estimand described above.

9.7.3. Pain Endpoints

The principal pain endpoint (absolute change from baseline in total spinal pain**)** will be summarized as mean value at baseline and Month 3 and as mean change from baseline to Month 3, together with measures of variability and 95% CIs. CIs are provided for descriptive purposes and do not imply hypothesis testing.

Further details will be provided in the SAP.

9.7.4. Treatment Exposure and Persistence Analyses

Filgotinib exposure will be defined as total duration of filgotinib treatment, calculated as last dose date of filgotinib minus first dose date + 1day, irrespective of any temporary interruptions, and expressed in weeks using up to 1 decimal place (e.g., 4.5 weeks).

Treatment patterns over follow-up will be described, including starting dose, dose modifications, temporary interruptions, treatment restart, concomitant axSpA-related medication, treatment switching, and permanent discontinuation. Reasons for discontinuation will be summarised using predefined categories and described overall and, where relevant, referring to the timepoint of the follow-up visit.

Treatment persistence rate will be assessed at 3, 6, 12, 18 and 24 months after treatment initiation and defined as the proportion of patients remaining on filgotinib at the respective time point. The probability (95% CIs) and number of patients discontinuing filgotinib will be provided. Time to permanent treatment discontinuation will be analysed using Kaplan-Meier methods, and persistence probabilities with 95% CIs will be presented graphically and in tabular form.

Exploratory Cox proportional hazards models will be used to analyze persistence and to model the prognostic effect of selected covariates (including sex, body mass index (BMI), disease duration, and number of previous bDMARDs).

Joint models for time to treatment discontinuation and longitudinal outcomes may be used to characterize the association between treatment persistence and early improvements in pain and other outcomes.

9.7.5. Secondary and Exploratory Effectiveness Endpoints

Disease activity and clinical response at 3, 6, 12, 18, and 24 months will be assessed using ASDAS and will be described as mean change from baseline in ASDAS. BASDAI response and BASFI improvement will also be summarized. Peripheral and extra-musculoskeletal manifestations will be described as new-onset events, flares in pre-existing manifestations, and resolution rates.

9.7.6. Patient-reported Outcomes

Patient-reported outcomes including pain (total spinal pain, nocturnal spinal pain, painDETECT, WPI), disease activity and physical function (ASDAS, BASDAI, BASFI), anxiety and depression (HADS), and overall health status (ASAS-HI, PASS) will be calculated according to their respective algorithms, and mean changes from baseline will be provided for all routine visit windows.

9.7.7. Minimum Clinically Important Improvement and Responder Definitions

Clinically meaningful improvement will be assessed using endpoint-specific responder definitions. For NRS-based pain outcomes, including total spinal pain, nocturnal spinal pain, responder analyses will primarily use a decrease of ≥2 points on the 0–10 NRS at the respective timepoint as the main threshold for clinically meaningful improvement. This is consistent with published Minimum Clinically Important Improvement (MCII) estimates for pain and other general rheumatology outcome measures, for which an absolute improvement of approximately 15/100 or 2/10 and a relative improvement of approximately 20% have been proposed [30].

Patient Acceptable Symptom State (PASS) will be assessed directly in this study using a dichotomous yes/no item and will be analysed as the proportion of patients reporting an acceptable symptom state. Separately, for NRS-based pain outcomes, supportive summaries may describe the proportion of patients achieving an acceptable pain state.

Responder definitions will be based on established instrument-specific thresholds where available and clinically appropriate; otherwise, outcomes will be summarized primarily as continuous change from baseline. Further details will be specified in the SAP.

9.7.8. Safety Analyses

Summaries of adverse drug reactions, adverse events of interest, important identified and potential risks, pregnancies and deaths will be provided as counts, percentages, and rates with 95% CIs.

9.7.9. Missing Data

Patterns of missing data will be determined to identify the appropriate analytical methodology [49]. Missing outcome data due to intercurrent events (e.g., study withdrawal after treatment discontinuation) will be assessed and addressed in line with the estimand strategies described above. Imputation methods will be used to account for missing values in the dataset adhering to current European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidelines. Multiple imputation may be used, in particular for multivariable analyses and sensitivity analyses, prior to carrying out multivariable analyses. A complete case analysis (patients with all variables present) will also be used.

9.7.10. Subgroup Analyses

Analyses and descriptive statistics of outcomes (primary, secondary, and exploratory) will be reported for all patients together and by clinically relevant subgroups e.g.: disease classification (r-axSpA vs. nr-axSpA), disease duration (early disease ≤2 years vs. established disease >2 years), prior bDMARD exposure (bDMARD-naïve vs. bDMARD-experienced), type or

mechanisms of prior advanced therapy, presence of peripheral manifestations (yes vs. no), presence of EMMs (yes vs. no), and baseline disease activity (moderate vs. high). Country-specific analyses will also be performed if the number of patients enrolled in each country allows this.

Further details of the data analysis, handling of missing data, and sensitivity analyses will be provided in the SAP.

9.8. Quality Control

To ensure the quality and integrity of the study results, the EDC system will include automatic data validation checks. The sponsor and/or contracted third party vendor will perform remote manual data quality review in accordance with the study data quality and monitoring documents. In addition, study monitors will engage sites with regard to data quality and completeness via telephone calls and may perform onsite visits, as documented in the study monitoring plan. The investigator agrees to respond to the resulting queries in a timely manner to enable the collation of data.

This study will be conducted in accordance with the guidelines for Good Pharmacoepidemiology Practices (GPP) and Good Pharmacovigilance Practices (GVP), including archiving of essential documents.

9.9. Limitations of the Research Methods

The assessment schedule was designed to balance scientific sensitivity to early treatment effects with feasibility in routine care and consistency with the recall periods of the selected instruments.

Filgotinib initiation represents a clinically meaningful ‘decision point’ at which patients and physicians expect rapid symptomatic change, particularly in spinal pain. Capturing the trajectory – not just a single follow-up value – therefore requires dense early measurement. A short daily diary during Days 1-7 is justified because it provides sufficient temporal resolution to describe onset and early dynamics of pain and related symptoms (including nocturnal pain), while remaining short enough to preserve adherence and limit reactivity. The schedule then transitions to monthly assessments until the end of study to bridge the high-frequency initiation phase with routine follow-up and to support interpretation of the Month 3 routine-care visit, where early benefit is formally evaluated.

After the high-frequency initiation phase (daily ePRO in the first week and thereafter weekly until week 4), the study transitions to monthly completion of the short 9-item ePRO battery until the end of study. Monthly remote assessments provide an optimal balance between scientific value and feasibility in routine care: they are frequent enough to characterize the durability of early symptomatic benefit, detect fluctuations and potential loss of response, and describe the multidimensional patient impact (pain, fatigue, stiffness, sleep and function) without requiring additional on-site visits. Finally, monthly assessments reduce patient burden compared with continued weekly questionnaires, which is expected to improve adherence over long follow-up and strengthen the validity of trajectory- and predictor-analyses under real-world conditions.

This study has the characteristic limitations of non-interventional studies, for example selection bias, information bias, confounding, and missing values.

In order to reduce selection bias, patients' eligibility criteria have been well defined. Eligible patients are approached consecutively for participation, and inclusion is contingent on provision of informed consent. Risk of selection bias remains present, e.g., due to the choice of sites that contribute patient data. However, a selection of sites in multiple countries will help reduce this kind of bias. The use of electronic devices rather than paper to capture PROs may also introduce a selection bias into the study population.

This study is a non-comparative, non-interventional study, in which treatment is determined by routine clinical practice. To reduce the impact of confounding in comparative analyses (e.g., by dose), key patient and disease characteristics as well as relevant treatment history will be collected and considered in the analyses. Multivariable analyses will be used to adjust for measured confounders; where appropriate, additional sensitivity analyses will be performed. Information bias will be minimized through standard measurement instruments, a structured eCRF, and site training.

A primarily electronic PRO approach, completed by patients at home within predefined time windows around the scheduled study visits, is scientifically and operationally justified. Patients will complete the PRO questionnaires electronically, preferably on their own device, using a simple guided access procedure, such as a QR code or link and brief instructions. This approach allows patients to complete the questionnaires in a familiar environment, reduces site workload, enables time-stamped entries, allows reminders, and supports completion close to the intended visit window. These features are particularly important for time-sensitive symptom assessments, such as pain intensity and nocturnal pain, where same-day or recent-period reporting helps to minimise recall bias and improves the validity of trajectory endpoints.

For the full visit-related questionnaire battery, patients will have a predefined completion window extending several weeks before and after the scheduled physician visit. This flexible window reduces time pressure, allows patients to complete the questionnaires at home and at their own pace, and provides an opportunity for a second attempt in case of technical or practical difficulties.

Paper questionnaires will be available only as a backup option if electronic completion is not feasible, for example due to technical difficulties, lack of device access, limited digital literacy, or patient-specific barriers to using the electronic system. This backup option is intended to preserve inclusiveness and minimise selection bias or differential missingness, while maintaining electronic data capture as the preferred and standard mode of PRO collection.

Adequate patient onboarding and practical support by site staff will be important. Site staff should explain the purpose of the PRO assessments, provide clear instructions for electronic completion at home within the defined visit window, ideally before the clinical visit, assist with access or navigation where needed, and reinforce the importance of complete and timely responses.

This primarily electronic strategy, supported by paper backup only when necessary, aims to maximise data quality for time-sensitive endpoints while preserving representativeness and avoiding systematic exclusion of patients who cannot use, or have substantial difficulties using, electronic devices.

9.10. Other Aspects

9.10.1. Access to Information for Monitoring

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the forms. The investigator may provide the study monitor with access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.10.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.10.3. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory agencies and IEC/ IRB Review, where applicable.

10. PROTECTION OF HUMAN PATIENTS

This study will follow the guidelines of the World Medical Association's Declaration of Helsinki in its revised edition [50] and any applicable national guidelines, laws and regulations.

10.1. Data Privacy

All personal data are treated as strictly confidential by the investigator, the staff of the CRO, the Sponsor, and any authorized third parties involved. Processing is carried out in full compliance with Regulation (EU) 2016/679 (GDPR).

Personal data are protected through appropriate technical and organizational measures designed to prevent unauthorized access, disclosure, alteration, loss, or unlawful processing. Access is limited to authorized personnel strictly on a need-to-know basis, all of whom are bound by confidentiality obligations.

Data are stored in secure IT systems (protected by passwords, antivirus software, and firewall systems) and, where in paper form, kept in locked archives accessible only to authorized personnel. Equivalent data protection and confidentiality safeguards are contractually required for third parties, under the oversight of internal audit and compliance functions.

Participants' identification data are replaced with codes (pseudonymization) and can only be re-identified by the investigator, who securely retains the identification key.

The Sponsor acts as Data Controller for the personal data collected within the study and processes such data in accordance with applicable data protection laws and for purposes strictly related to the conduct of the clinical study.

10.2. Good Pharmacoepidemiology and Pharmacovigilance Practices

The study will be conducted in accordance with directives, guidelines on Good Pharmacoepidemiology [51] and Good Pharmacovigilance Practice (GVP) [52], and local regulatory requirements, as applicable.

10.3. Independent Ethics Committee (IEC)/Institutional Review Board (IRB) Review

The sponsor (or the investigator) will submit this protocol and any accompanying material to be provided to the patient (such as patient information sheets, or descriptions of the study used to obtain informed consent) to an IRB or IEC as applicable. The investigator will not begin any study patient activities until approval from the IRB or IEC has been documented and provided as a letter to the investigator. The approval document must be dated and clearly identify the study and the related study documents being approved, if applicable.

The initial protocol and any subsequent modifications made to the protocol or any accompanying material to be provided to the patient after initial IRB or IEC approval will also be submitted for IRB or IEC approval prior to use, with the exception of those necessary to reduce immediate risk to study patients.

10.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each patient participating in this study after adequate explanation of the aims, methods, objectives, and alternatives of the study prior to study participation and before performing any study-related activities. The investigator must utilize the most current IRB or IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

The Sponsor is established in Italy and operates in compliance with applicable European data protection laws. As Data Controller, the Sponsor provides the data subject with a Privacy Notice pursuant to Article 13 GDPR, outlining how personal data are processed.

The Privacy Notice includes, in particular: the identity and contact details of the Controller (and its representative, where applicable) and of the Data Protection Officer; the purposes and legal bases of processing; the categories of recipients of the personal data; any transfers to third

countries or international organizations and the applicable safeguards; the applicable data retention period (or criteria used to determine it); and the data subject's rights.

These rights include the right to access, rectify, erase or restrict processing of personal data, to object to processing, and to data portability, as well as the right to withdraw consent at any time (where processing is based on consent), without affecting the lawfulness of processing prior to withdrawal, and the right to lodge a complaint with a supervisory authority.

10.5. Personal Data Breach

Any personal data breach shall be reported to the Sponsor without undue delay and, in any event, within 48 hours from becoming aware of the incident, using the designated Incident Management process.

The notification shall, to the extent possible, include the nature of the breach, the categories and approximate number of data subjects and data affected, the type of incident and data involved, the timing (occurrence and detection), and the relevant contact details.

The reporting party shall cooperate with the Sponsor and provide any additional information required to support assessment, mitigation, and compliance with applicable data protection obligations.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This study is a post-authorization, prospective, non-interventional study and will collect all required safety information in line with requisite global requirements.

11.1. Definitions

11.1.1. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product that is noxious and unintended. An ADR is also known as a 'side effect'.

An ADR can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, considered potentially related to the medicinal product. AEs may also include overdose, drug abuse/misuse reports, or occupational exposure.

An ADR does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and should be reported.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed will be considered a preexisting condition and should be documented in the medical history section of the CRF, if applicable.
- Worsening or clinically relevant change in a pre-existing condition after initiation of filgotinib should be assessed by the investigator. It should be reported as an ADR only if a causal relationship with filgotinib is suspected. Otherwise, it should be documented as part of the patient's medical history or clinical course, as applicable.

11.1.2. Serious Adverse Drug Reaction

A serious adverse drug reaction (SADR) is defined as any serious adverse event that is considered causally related to the medicinal product at any dose administered.

A SADR is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, suspected transmission of an infectious agent via a contaminated medicinal product is considered a medically important event and must be reported in accordance with the applicable expedited reporting requirements.

11.1.3. Special Situations Reports

Special situation reports include reports of abuse, drug interactions, counterfeit or falsified medicine, exposure via breastfeeding, medication error, misuse, occupational exposure, off-label use, overdose, pregnancy, transmission of infectious agents via the product, and unexpected benefit. Definitions and examples are provided below:

- Abuse: Persistent or sporadic intentional excessive use of a medicinal product by a patient.

- Drug interactions: Any reports of drug/drug, drug/food, or drug/device interactions.
- Counterfeit or falsified medicine: Any medicinal product with a false representation of: a) its identity, b) its source, or c) its history.
- Exposure via breastfeeding: Reports of any exposure to a medicinal product during breastfeeding.
- Medication error: Any unintentional error in the prescribing, dispensing, preparation for administration, or administration of a medicinal product while the medication is in the control of a healthcare professional, patient, or consumer.
- Misuse: Use of a medicinal product that is intentional and/or inappropriate, and not in accordance with its authorized product information.
- Occupational exposure: Exposure to a medicinal product as a result of one's professional or non-professional occupation
- Off-label use: Where a medicinal product is intentionally used by a health care professional for a medical purpose not in accordance with the authorized product information with respect to indication, dose, route of administration, or patient population (e.g., the elderly).
- Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose in the product labeling.
- Pregnancy reports (maternal pregnancy and partner pregnancy): Reports of pregnancy following maternal or paternal exposure to the product.
- Product complaint or quality defect of medicinal product: Complaints or defects of the medicinal product arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.
- Unexpected benefits: An unintended therapeutic effect where the results are judged to be desirable and beneficial.
- Transmission of infectious agents via the product: Any suspected transmission of an infectious agent through the medicinal product.

11.1.4. Adverse Events of Interest

Under treatment with JAKi including filgotinib, patients may potentially experience adverse events that warrant close monitoring.

These include:

- Serious and opportunistic infections (including herpes zoster)
- Major adverse cardiovascular events (MACE)
- Venous thromboembolism (VTE)
- Hyperlipidemia
- Malignancies excluding NMSC

- Non-melanoma skin cancer (NMSC)
- Gastrointestinal (GI) perforation
- Fractures

11.2. 11.1Scope of Safety Data Collection

11.2.1. Safety Events to be Collected

The ADR reporting period for safety surveillance begins when the patient signs the ICF and ends at the patient's last follow-up visit or contact. Safety information to be collected includes a description of the safety event, start and stop dates, severity, causality, and other relevant medical information.

Safety events to be collected include:

- Deaths
- All ADRs (serious and non-serious)
- All AEIs, as listed in Section 11.1.4
- Any Special Situation Reports (SSRs)

If needed, the sponsor may request additional follow-up information for the safety event.

In case an ADR or AEI is ongoing at the time of the last follow-up visit, the investigator needs to follow-up on the patient until resolution or reasonable stabilization and to document it in the patient's source documentation. No related updates or additional data on the ADR or AEI should be reported in the eCRF.

After the patient's last follow-up visit or last study-related contact, no further active study-specific safety data collection will be performed.

However, if an ADR, AEI, pregnancy, or other reportable safety information becomes known to the investigator or site after this time and is suspected to be related to filgotinib, it should be forwarded to the Sponsor's Pharmacovigilance department as a spontaneous post-study report in accordance with routine pharmacovigilance requirements.

11.2.2. Process for Recording and Reporting to Sponsor

Site personnel must record ADR, AEIs, special situations (including pregnancies), and deaths through the safety reporting form (eCRF). Detailed instructions can be found in the eCRF completion guidelines.

If it is not possible to submit the safety information electronically to the sponsor's Pharmacovigilance (PV) department:

- Record the event on the Safety Reporting Form (available in the study binder) and send it to sponsor PV.

- As soon as it is possible to do so, any safety event reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

During the conduct of the study, the sponsor may change the mode of transmission of safety information after informing the site of the change.

Sponsor PV contact details are given in the study binder.

11.2.3. Instructions for Reporting Pregnancies

The following information is required to be collected and reported for this study if a patient becomes pregnant while taking filgotinib and/or if a female partner of a male patient becomes pregnant while the male patient is taking filgotinib:

- Information on all pregnancies.
- The outcome of the pregnancy, including any premature termination (e.g., a spontaneous abortion or an induced therapeutic abortion due to complications or other medical reasons).

Pregnancy information and pregnancy outcome should be reported through safety reporting form on the EDC. Timelines for reporting to sponsor are provided in Table 4.

Any premature termination of pregnancy (e.g., a spontaneous abortion or an induced therapeutic abortion due to complications or other medical reasons) or SADR occurring as an adverse pregnancy outcome post-study must be reported within 2 calendar days.

11.3. Responsibilities of Investigators

Investigators (or delegated site staff) are responsible for detecting, documenting, and reporting the safety information described in Section 11.2.1, according to this protocol and applicable local requirements [52]:

- All relevant clinical information must be recorded in the source documents and transcribed to the CRF, including event description, onset and end dates, seriousness criteria, severity, outcome, actions taken, and assessment of causality in relation to the medicinal product(s).
- Investigators must actively follow up SAEs and clinically significant non serious ADR/AEIs until resolution, stabilization or return to baseline, or until sufficient information is obtained to allow an adequate assessment of causality and outcome .
- Investigators must provide additional information to the sponsor upon request to support regulatory reporting and signal evaluation.

It is the responsibility of the Investigator to report safety events not related to filgotinib, but related to concomitant treatments as per local requirements (local regulatory body or MAH of the concomitant treatment).

11.4. Reporting Procedures and Timelines

11.4.1. Reporting from Investigator to Sponsor

Timelines for reporting to the sponsor PV are provided in

Table 4. All timelines depicted below are in relation to the investigator's awareness of the respective event.

Table 4. Overview of Timelines for Reporting of Safety Information

Event category*	Timeline
Death irrespective of relationship to filgotinib	Report to sponsor PV via the eCRF **within 24 hours.**
ADR, with positive causal relationship to filgotinib	**Non-serious:** Report to sponsor PV via the eCRF **within 7 calendar** days. **Serious:** Report to sponsor PV via the eCRF **within 2 calendar days** (within 24 hours for fatal or life-threatening events).
AEI, irrespective of relationship to filgotinib	Non-serious: Report to sponsor PV via the eCRF **within 7 calendar** days. Serious: Report to sponsor PV via the eCRF **within 2 calendar** days (within 24 hours for fatal or life-threatening events).
Special Situations	Report to sponsor PV and enter into the eCRF **within 15 calendar days****
Pregnancy reports	Report to sponsor PV within **15 calendar days** of knowledge of the pregnancy** Report to sponsor PV within **2 calendar days** of knowledge of all pregnancy related serious events (regardless of causality, e.g., a spontaneous abortion, hospitalization, etc.).**
* Reporting to health authority will be performed by sponsor as per applicable regulations. ** Using the safety reporting form.	
Safety events not related to filgotinib: it is the responsibility of the Investigator to report safety events not related to filgotinib, but related to concomitant treatments as per local requirements (local regulatory body or MAH of the concomitant treatment).	

11.4.2. Reporting from Sponsor to Authorities

The sponsor will manage and report suspected adverse reactions from this study in accordance with EU pharmacovigilance legislation and GVP Module VI, including electronic reporting of individual case safety reports (ICSRs) to EudraVigilance and, where required, to national competent authorities (GVP Mod VI).

- For solicited reports from non-interventional post-authorization studies with systematic collection of suspected adverse reactions, ICSRs will be reported as follows:
    - Serious suspected adverse reactions: expedited reporting within the applicable regulatory timeframes (e.g., 15 calendar days from day 0) (GVP Mod VI).
    - Non-serious suspected adverse reactions: submission in accordance with GVP Module VI and EU requirements for non-serious ICSRs (e.g., within 90 days), if applicable (GVP Mod VI).

11.5. Causality, Seriousness, and Severity Assessment

Investigators will provide an assessment of seriousness and causality for each AE, using the criteria above and their clinical judgement (GVP Mod VI).

- Causality will be classified (e.g., not related, unlikely, possibly, probably, or certain) according to the MAH's standard causality assessment guidance; events with at least a reasonable possibility of a relationship will be considered suspected adverse reactions (GVP Mod VI).
- Severity (mild, moderate, severe) reflects the intensity of the event and is distinct from seriousness; both must be assessed and documented separately (GVP Mod VI).

The MAH will perform a medical review of SAEs/SARs and may revise the causality or seriousness assessment, documenting the rationale in the safety database, in accordance with current procedures (GVP Mod VI).

11.6. Data Management, Confidentiality, and Quality

Safety data will be entered into validated systems and integrated into the MAH pharmacovigilance database for scientific evaluation, signal detection, and regulatory reporting, in accordance with GVP Module VI and the sponsor's pharmacovigilance system master file (GVP Mod VI).

- The safety reporting system will ensure that collected reports are authentic, accurate, complete, verifiable, and submitted within the required timelines (GVP Mod VI).
- Personal data will be processed in compliance with applicable data protection legislation (e.g., GDPR) and national laws; only coded identifiers will be used in safety reports submitted to authorities, without directly identifiable patient information (GVP Mod VI).

11.7. Aggregate Safety Evaluation

Safety data from this study will contribute to the periodic benefit-risk evaluation of the medicinal product(s), including periodic safety update reports (PSURs) or other aggregate reports, in line with EU pharmacovigilance requirements (GVP Mod VI).

11.8. Clinical Laboratory Abnormalities

Laboratory abnormalities without clinical significance are not recorded as safety events. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to drug interruption, modification, or discontinuation and considered to be causally associated with the medicinal product must be recorded as an ADR. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an ADR if they meet the definition of an ADR as described in Section 11.1.1. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

The investigator or qualified sub-investigator is responsible for assessing the causal relationship to drug therapy for each event and using clinical judgment and the following considerations:

- No: Evidence exists that the AE has an etiology other than the drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- Yes: There is a reasonable possibility that the event may have been caused by the medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of reporting safety information.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication and/or posted in a publicly accessible database of study results complying with applicable sponsor standards.

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ANNEXES

Annex 1: List of Stand-alone Documents

None

Annex 2: ENCePP Checklist for Study Protocols

Not applicable for non-PASS

Annex 3: Additional Information

None.