ARTEMIS
Women's Health
Foundation

In collaboration with Catenion

White Paper

Endometriosis and Adenomyosis Stakeholder Roundtable

Mind the Gap(s): Moving Novel Drugs from Bench to Bedside

ARTEMIS Women's Health Foundation

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1 PREFACE

1.1 Background on Roundtable & White Paper

Endometriosis (EM) affects over 10% of all women over the course of their lives, predominantly impacting those 20-50 years of age – a critical period encompassing their peak professional and reproductive years. This timing significantly amplifies the disease's impact on overall quality of life, professional development, and family planning. Despite its prevalence and far-reaching consequences, the only approved therapies for EM (other than analgesics) are hormonal in nature. More recently introduced hormonal treatments offer improved efficacy, safety and/or convenience. However, there remains a lack of effective, non-hormonal therapies to treat patients whose disease is not adequately controlled with the current standard of care, those who want or need to avoid hormonal treatments and those with a desire to get pregnant. Adenomyosis (AM) presents a pharmaceutical "white space" since there are currently no approved therapies at all.

Several recent developments have the potential to provide new momentum to EM drug development. These include novel mechanisms of action (MoAs) and modalities, as well as an increased focus on improving the lives of patients beyond pain relief. Together with new diagnostic methods in development, the diagnosis and treatment of endometriosis could significantly change over the next decade. However, the move from hormonal to non-hormonal drugs and from symptomatic to disease-modifying therapies will require a revision of the status quo in terms of clinical development, regulatory frameworks and market access.

To address these topics, the Artemis Women's Health Foundation ("Artemis"), a non-profit foundation focused on accelerating innovation in Women's Health, joined forces with Catenion, a science-driven management consulting firm serving the biopharma sector. Over a period of several months, Artemis and Catenion engaged with a range of stakeholders, through a series of conversations, culminating in a half-day Roundtable discussion held in Basel, Switzerland on April 15th, 2024. The participants represented various groups, including pharmaceutical and startup companies, patients, academic and clinical key opinion leaders (KOLs), as well as experts in clinical development, regulatory affairs, and market access from the US and Europe.

In this White Paper, our goal is twofold: On the one hand, we aim to provide guidance to scientists and entrepreneurs pursuing innovative approaches for the treatment of EM and/or AM. On the other hand, we want to highlight systemic gaps - across data resources, research tools, regulatory guidance and market access frameworks - that should be addressed to unleash and incentivize a broader wave of innovation for these important diseases.

1.2 Overview and Scope

This White Paper focuses on the clinical development, regulatory path and market access challenges for new non-hormonal treatment options targeting EM and AM beyond addressing pain. A detailed discussion of the pathophysiology of these diseases and the current treatment guidelines in different geographies is beyond the scope of this document, but we point to relevant literature in the "Key References" section.

This document aims to integrate perspectives of patients, physicians, startups and pharmaceutical companies, as well as regulators and payers. Its goal is to raise awareness about the urgent need for action, facilitate discussions and identify gaps that need to be addressed collaboratively. By addressing these key areas, this White Paper seeks to catalyze research and development of new disease modifying treatment options, thus improving the lives of the women affected by this highly prevalent yet historically underfunded disease.

2 INTRODUCTION

2.1 About Endometriosis and Adenomyosis

Both endometriosis (EM) and adenomyosis (AM) are chronic and often painful conditions that significantly impact a woman's quality of life.

EM is a condition where tissue similar to the endometrium (i.e. the tissue lining the inside of the uterus) starts to grow outside the uterus. It typically affects pelvic organs but can also appear in other areas of the body. This condition is estimated to impact roughly 10% of women of reproductive age, translating to an estimated 190 million women worldwide.

Despite its prevalence, EM remains an indication with significant unmet medical needs, accentuated by its unclear etiology, variable symptoms, and frequent long delays in diagnosis. While EM symptoms often begin in adolescence around the start of menstruation, the average age at the time of diagnosis tends to be much later, commonly in the 30s. The complexity of the condition, combined with inadequate diagnostic and treatment options, underscores the pressing need for further research and improved therapeutic strategies.

While the revised American Society for Reproductive Medicine (rASRM) staging system and the phenotypic classification based on lesion sites are commonly used to categorize endometriosis patients, their clinical utility is limited. The rASRM system, though widely adopted, does not adequately correlate with symptom severity or fertility outcomes. For instance, some patients with stage I endometriosis may experience severe pain, while others with stage IV might have milder symptoms. This discrepancy suggests that factors beyond visible lesions, such as inflammation, nerve infiltration, and central sensitization, significantly influence pain symptoms in endometriosis patients.

The phenotypic classification, which categorizes endometriosis into superficial peritoneal (SPE), ovarian endometrioma (OMA), and deep infiltrating endometriosis (DIE), provides more descriptive information about lesion locations. However, it does not fully capture the complexity of the disease or predict clinical outcomes.

Furthermore, neither classification system adequately addresses differences in etiology, provides comprehensive prognostic information, or predicts treatment response. These limitations highlight the need for a new, more comprehensive classification approach that considers not only the anatomical extent and symptomatic impact of the disease but also factors that may indicate treatment responsiveness. Such a system would enable more personalized and effective therapeutic strategies for endometriosis patients.

This document aims to integrate perspectives of patients, physicians, startups and pharmaceutical companies, as well as regulators and payers. Its goal is to raise awareness about the urgent need for action, facilitate discussions and identify gaps that need to be addressed collaboratively. By addressing these key areas, this White Paper seeks to catalyze research and development of new disease modifying treatment options, thus improving the lives of the women affected by this highly prevalent yet historically underfunded disease.

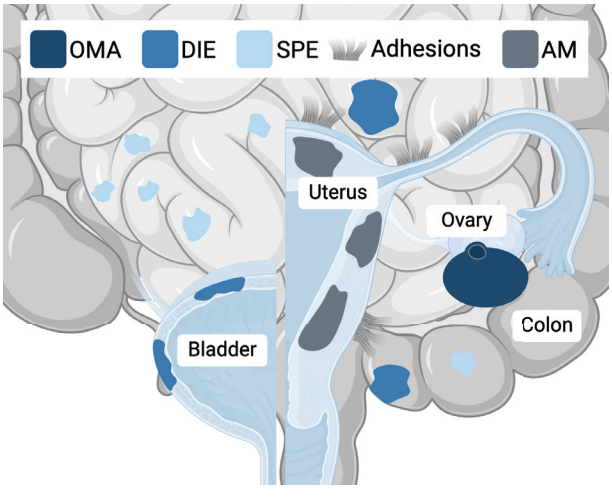

Figure 1: EM staging is based on the location, extent and depth of disease, but little is known about progression, and the number, size and location of lesions do not correlate well with the severity of symptoms. Organs not to scale

For women today resorting to surgery, such as (repeated) laparoscopies or even hysterectomy, the need for more effective pharmacological treatment options is particularly pressing. These surgical interventions can have a long-lasting impact on women's quality of life and reproductive health. Adhesions (bands of scar tissue that may form after surgery) can cause pelvic pain, infertility and bowel obstructions. Hysterectomy and/or ovariectomy (i.e. surgical removal of the uterus and ovaries, respectively) can result in a range of complications, including reduced ovarian reserves, hormonal changes and sexual problems, particularly for women undergoing the procedure at a younger age. And while these procedures reduce/eliminate childbearing potential, they may not altogether resolve EM since ectopic endometrial tissue may be left behind.

While EM is the primary focus of this paper and has been researched more, adenomyosis (AM) shares certain characteristics, complications and treatment approaches.

AM is a condition where endometrial-like tissue is present inside the myometrium (i.e. the muscular wall of the uterus). Although AM and EM frequently coexist in a subset of patients, they are currently regarded as separate diseases. AM can cause severe cramping, heavy bleeding, and other symptoms that can significantly impact a woman's quality of life. AM is estimated to affect up to 20-35% of women, making it a common gynecological condition. Like EM, AM is underdiagnosed and poorly understood, often diagnosed even later in life than EM, leading to delays in treatment and significant distress for those affected. Unlike EM, AM can be diagnosed through diagnostic modalities, especially transvaginal ultrasound (TVUS). There are today no approved drugs for the treatment of AM in the US and EU5.

2.2 The Patient Perspective

For millions of patients, EM manifests as cyclical or chronic pelvic pain, with or without infertility, impacting various aspects of women's lives from adolescence to menopause. Patients often have to consult multiple physicians before receiving a definitive diagnosis. Societal biases regarding pain in women, particularly in non-white populations, further complicate matters. In addition, despite existing guidelines, patients may face heterogeneous treatment approaches in practice.

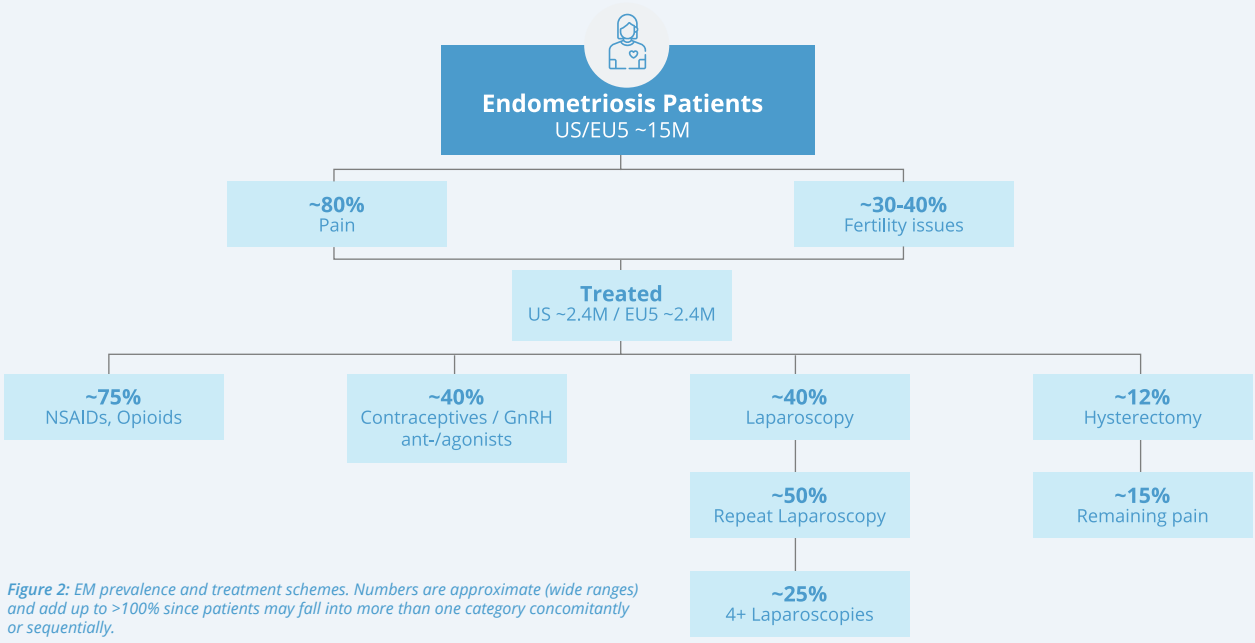

Figure 2: EM prevalence and treatment schemes. Numbers are approximate (wide ranges) and add up to >100% since patients may fall into more than one category concomitantly or sequentially.

Current treatment options are frequently inadequate due to limited efficacy, restricted access, or incompatibility with the desire for pregnancy. Patients generally have two primary unmet needs: effective pain management and the ability to have children. Problems include inadequate options for pain management in non-responsive patients, a lack of non-hormonal therapies for infertile patients, and the high costs and limited availability of procedures like IVF and laparoscopic surgery, creating access barriers for many patients. Paradoxically, widely used current treatments, rather than restoring fertility, prevent pregnancies (oral contraceptives) or may temporarily mimic a postmenopausal state (GnRH agonists/antagonists).
The most common and overlapping symptoms and key health issues of EM patients include:

- Dysmenorrhea (painful periods)
- Non-menstrual pelvic pain (NMPP)
- Lower back pain during periods
- Dysuria (pain with urination)
- Dyschezia (pain with bowel movements)
- Dyspareunia (pain during intercourse)
- Infertility
- Heavy bleeding
- Fatigue, nausea, bloating

EM is a leading cause of infertility, affecting up to 50% of infertile women. This creates a difficult situation for EM patients desiring pregnancy, as they must discontinue medications that provide pain relief and symptom management during their fertility journey. The inability to use hormonal treatments while pursuing a pregnancy can exacerbate the already severe pain and symptoms experienced by these patients.

Figure 3 shows different, highly simplified, exemplary patient journeys, highlighting the frequency of pain experienced by EM patients. An inadequate or absent response to medical treatments, will lead to escalating therapeutic interventions, with laparoscopic surgery (and ultimately hysterectomy) as potential next steps.

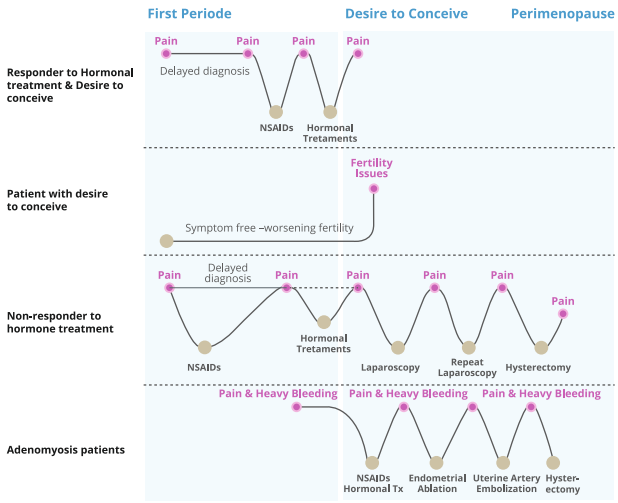

Figure 3: Illustrative EM and AM patient journeys

Around 20-25% of EM and 50-70% of AM cases are asymptomatic or „silent", with unexplained infertility being the only symptom experienced. In these patients, there is (initially) no overt pelvic pain or other symptoms typically associated with these conditions. Proper diagnosis of these asymptomatic cases is crucial, as leaving them untreated can allow disease progression affecting other pelvic organs and worsening fertility problems over time.

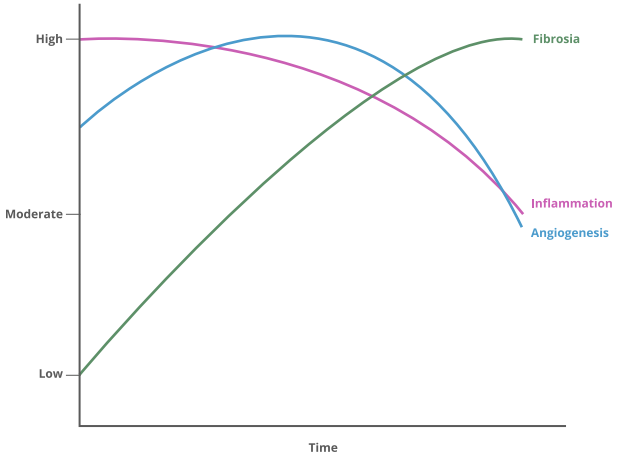

Figure 4: Illustrative levels of inflammation, angiogenesis, and fibrosis in EM. AI-generated summary of current knowledge, hypotheses mentioned during interviews.

2.3 New Targets & Mechanisms of Action

In the past, the treatment of EM has largely been limited to a small number of molecular targets and mechanisms of action (MoAs), based on the understanding that it is an estrogen-driven inflammatory disease frequently causing pain.

Traditionally, the following drugs therefore represent the standard of care (SoC):

- Analgesic medications (NSAIDs, opioids)
- Hormonal agents (e.g. contraceptives, progestagens; GnRH agonists/antagonists)

More recent research has revealed that inflammation, angiogenesis, and fibrosis play crucial roles in the development and progression of endometriotic lesions from the earliest stages of the disease. Inflammation promotes the growth and survival of ectopic endometrial tissue, while angiogenesis supplies the necessary blood flow to sustain these lesions. Fibrosis is recognized as an integral part of EM pathogenesis, it contributes to the formation of adhesions and scarring, further exacerbating pain and infertility. This fibrotic process begins early, creating a pro-fibrotic environment that drives disease progression.

Efforts are under way to elucidate the molecular pathophysiology of EM, paving the way for the development of novel targeted therapies. Genomic and proteomic studies have already identified certain key pathways and molecules involved in the disease process. These pathways regulate functions such as inflammation, cell proliferation, invasion and angiogenesis, which drive the development and progression of endometriotic lesions.

However, translating these findings into effective targeted therapies remains a significant challenge. Current preclinical in vitro and animal models have important limitations and fail to fully represent the complex pathophysiology of EM. Incorporating and monitoring clinically relevant endpoints like pain and infertility is challenging. The models may therefore not accurately represent the disease stage or lesion heterogeneity, limiting their predictive value. Researchers are also developing advanced organoid and organ-on-chip models to complement existing animal models, especially for screening.

Currently available treatments primarily address symptoms rather than targeting the underlying pathophysiology. Since the exact etiology and pathophysiology of EM are still poorly understood, no non-hormonal drugs have so far gained approval. However, genetic studies have provided insights into the molecular subtypes of EM, which could guide the development of personalized therapies in the future. As of today, several drugs with new MoAs are in clinical development:

Mechanism (administration)	Drug (sponsor)	Status	Comment
mPGES-1 inhibitor (oral)	Vipoglanstat (Gesynta Pharma)	Phase 2	Analgetic and anti-inflammatory MoA; inhibiting prostaglandin E2 synthase (mPGES-1)
HSD17B1 inhibitor (oral)	OG-6219 (Organon, ex-Forendo)	Phase 2	Endocrine MoA; reducing estradiol production in EM lesions
anti-IL-8 antibody (injectable)	AMY109 (Chugai)	Phase 2	Anti-inflammatory MoA; binding IL-8 involved in inflammation & fibrosis
anti-IL-33 antibody (injectable)	MT-2990 (Mitsubishi Tanabe)	Phase 2	Immunologic MoA; binding IL-33 to modulate inflammation in EM lesions. Phase 2 results published on clinical-trials.gov.
PDHA1 activator (oral)	Dichloroacetate, DCA (University of Edinburgh)	Phase 2	Metabolic MoA; repositioned oncology agent modulating glucose metabolism
Lysosomal pH (?) (oral)	Hydroxychloroquine, HCQ (SLBST Pharma)	Phase 2	Immunomodulatory MoA; repurposed agent, exact MoA to be determined

Table 1: Selected clinical drug candidates with novel non-hormonal MoAs (Status: April 2024)

Other proposed mechanisms of action (eg. prostaglandin pathway, apoptotic, antibiotic) are in preclinical stages of validation, including assets from Maipl, FimmCyte, Temple Therapeutics, Endocyclic, Flightpath and Netris pharma.

Cross-disease perspectives: Precision medicine

The therapy of malignant tumors (e.g. breast cancer) and non-malignant diseases (rheumatoid arthritis, asthma, irritable bowel disease) was transformed by their molecular classification and introduction of "targeted therapies". In EM, such a "precision medicine" approach has so far not been possible, but experts believe that it will emerge over the coming years.

2.4 The Pharma/Biotech Perspective Opportunities & challenges in addressing unmet needs

Emerging companies (and some established players) are developing preclinical and clinical assets with novel MoAs aimed at reducing inflammation, modulating the immune system's response, decreasing lesion burden and alleviating pain. However, the historic translational and regulatory path from preclinical stages to approval is not well-suited for new, disease-modifying drugs, and EM is consequently seen as a risky indication by some investors and pharmaceutical companies. The recently launched class of oral GnRH antagonists improve on the previously available GnRH agonists by being orally available, easier to discontinue and offering a better side effect profile. However, their commercial launches have fallen short of the original optimistic projections, in part due to market access hurdles.

To address the unmet needs of patients with symptoms not adequately controlled by hormonal treatments and those with a desire to get pregnant, new diagnostic methods supporting non-invasive diagnosis, patient stratification, and monitoring of EM will be instrumental. Updating the current regulatory guidelines, including an array of acceptable endpoints and measurable parameters, will be essential to allow biotech and pharma companies to bring novel disease-modifying treatment options to patients. Additionally, payers need to be engaged early on to define the evidence needed to support adequate pricing and coverage decisions by insurers.

Cross-disease perspectives: Startup impact

The field of orphan diseases was transformed by startup companies, based on a confluence of scientific insights into diseases, new treatment modalities, entrepreneurs funded by VC firms, a favorable regulatory framework (eg tax credits, marketing exclusivity, fee waivers), an attractive market access environment for new drugs and high pricing.

Despite the aforementioned challenges, the successful development of a non-hormonal, disease-modifying drug for EM represents a massive commercial opportunity:

- EM affects an estimated 190 million women worldwide
- Potential for first-in-class or best-in-class therapies targeting novel MoAs beyond hormonal pathways, allowing for differentiation and fulfilling a major unmet need
- Improving disease management, quality of life, and fertility outcomes for patients suffering from chronic pelvic pain and infertility associated with EM
- Large overall patient population allows targeting subpopulations with particularly high unmet needs and/or high response rates to new MoAs

2.5 The Payer Perspective

From the perspective of healthcare payers (as well as healthcare systems and society), a non-hormonal, disease-modifying EM drug could provide both clinical and economic benefits, if properly used:

- **Cost-effective healthcare resource utilization:** More effective medical treatments aim to reduce the need for repeated surgeries, long-term healthcare interventions, emergency room visits for breakthrough pain, and potentially decreasing the need for costly fertility treatments. The quality-adjusted life year (QALY) gains may be comparable to treatments for other chronic conditions such as rheumatoid arthritis and multiple sclerosis, making improved EM therapies cost-effective interventions.
- **Significant economic impact:** EM affects women mainly between 20 to 50 years of age, impacting them at an important time during their professional, reproductive and family lives. By improving the management of EM, new therapies aim to reduce both absenteeism (i.e. absence from work) and presenteeism (i.e. reduced productivity while at work) of patients, thereby increasing workforce output and retention. This represents substantial value for employers and society.
- **Strategic treatment positioning:** New therapies are likely to be positioned as second/third line treatments, targeting patients inadequately served by current standards of care. This approach balances innovation with cost-containment, addressing payer concerns while offering important new options for patients with unmet needs.

However, to grant premium pricing, payers will require robust evidence that a new therapy provides durable disease modification, not just symptomatic relief.

- Cost-effectiveness data comparing drug costs to averted surgeries, complications, quality of life, productivity losses, and potential IVF cost savings will be important for reimbursement decisions.

3 ASPECTS OF DRUG DEVELOPMENT

3.1 General Considerations

Despite their efficacy, current hormonal therapies have various limitations, including their side effect profile and inability to effect disease modification or conceive pregnancies while on treatment (since they suppress ovulation). For novel non-hormonal treatments aiming to demonstrate a disease-modifying effect in EM and/or AM, it is crucial to engage regulatory agencies early on and to design a development path that takes future market access/commercial requirements into account, while being feasible from a clinical development and financial perspective.

Early engagement with regulatory agencies should focus on aspects such as:

- **Preclinical Efficacy and Safety:** MoA, efficacy, and safety (including reprotox) in relevant models
- **Biomarkers and Diagnostics:** Potential biomarkers or non-invasive tools to quantify lesion burden and disease progression
- **Inclusion Criteria:** Rationale for inclusion criteria and use of non-invasive diagnostics
- **Expanded Endpoints:** Including objective measures of disease burden, patient-reported outcomes beyond pain and/or fertility
- **Innovative Trial Designs:** Limitations of existing comparators and need for innovative designs based on new drugs' unique mechanisms

Involving a range of stakeholders, including patients, clinicians and researchers, in discussions with regulators will be essential in evolving the current drug development paradigms to better support the future approval of novel treatments while ensuring patient safety and access. Regulatory precedents exist in other indications for using non-invasive diagnostics in inclusion criteria and accepting endpoints beyond symptom relief to assess disease modification.

3.2 Diagnosis & Monitoring

In the past, neither biomarkers nor specific imaging tools have been available to confirm or rule out the diagnosis of small EM lesions. Since endometriotic lesions are typically located in the peritoneal cavity, the historic diagnostic gold standard is laparoscopy, an invasive surgical procedure, with or without histologic assessment of biopsies. This situation, combined with the often heterogeneous clinical symptoms, contributes to a situation where the diagnosis (and treatment) of EM is often delayed by many years. In recent years, new diagnostic modalities have begun to emerge, as shown below:

Method	Examples	Status	Use for diagnosis	Use for monitoring (of disease progression)	Comments
Laparoscopy		Established	Yes	(No)	invasive
Imaging	Ultrasound, MRI SPECT	In commercial use for DIE and OMA in development for SPE	Yes	Yes	improved resolution, novel image processing, use of targeted markers
In vitro diagnostics	Molecular markers in e.g. blood, saliva, menstrual effluent, uterine brush biopsy	In commercial use or development	(Yes)	(tbd)	Lacking validation in larger studies
Symptoms	Clinical diagnosis based on symptoms and physical examination	Established	Yes	(?)	subjective
Questionnaire	„Pain and Symptoms Diary"	Established	Yes	(?)	subjective

Table 2: Selected diagnostic modalities clinically used or in development (Status: April 2024)

Cross-disease perspectives: Role of diagnostics (1)

There is a well-documented interdependence between the development/availability of diagnostic tests on the one hand, and therapeutic options on the other. Examples from virology (HIV, HCV) and oncology demonstrate that improved diagnostic methods can be important drivers for the development and commercial success of therapeutics.

Cross-disease perspectives: Role of diagnostics (2)

In Alzheimer's disease, which is difficult to diagnose clinically, and where a definitive diagnosis was only possible postmortem, biomarkers and imaging were introduced for both patient inclusion into studies and as surrogate endpoints, allowing for the development and approval of new, disease-modifying drugs.

3.3 Patient Selection

Defining adequate inclusion criteria for clinical trials in EM and AM is crucial for estimating effect sizes, powering studies, ensuring efficient recruitment rates and informing later market access discussions, thereby laying the basis for clinical, regulatory and commercial success. These inclusion criteria of course need to align with a given drug's mechanism of action (MoA).

Patient Selection Criteria	Comments, Examples
Laparoscopically diagnosed EM	If the laparoscopic diagnosis occurred years prior to their enrolment, a patients' disease burden may have evolved in the meantime, increasing study population heterogeneity. Ideally, trials should enroll a representative real-world sample. Over-reliance on laparoscopic diagnosis risks selection bias and limited generalizability. A pragmatic approach using clinical symptoms, imaging, and laparoscopy when clinically indicated may be preferable.
Imaging findings	TVUS: widely available, but may be harder to document and objectively quantify; MRI, SPECT: reserved to specialty centers, possibly limiting recruitment
Patients awaiting laparoscopy	Measure the ability of drug treatment to delay surgical intervention(s). Caveat: May be hard to quantify, since driven by patient/physician preferences and local/individual access to surgical treatments. No existing data to calculate the sample size for a clinical trial.
EM types/subtypes	Location of EM (SPE, OMA, DIE) and/or AM lesions
	Lesion burden (mild, moderate, severe) caveat: subjective judgment
	Inflammatory vs fibrotic lesions

Patient Selection Criteria	Comments, Examples
Pain characteristics / severity	Dysmenorrhea, chronic NMPP, dysuria, dyschezia, dyspareunia; widespread versus localized pain
Point in patient journey	Before or after laparoscopy, non-responsive to pain and or hormonal treatments. A long EM history may result in chronified pain which is more difficult to control.
Fertility	Presence of infertility. May require controlling for other female & male factors

Others: Symptom severity, previous treatments (hormonal or surgical treatments), comorbidities (e.g. AM, IBS or IBD). Also, patients may reject wash-out period that can result in pain recurrence.

Table 3: Patient selection criteria

3.4 Endpoints

Current Limitations in EM Endpoints: The US Food and Drug Administration (FDA) currently considers pain relief as the only valid primary , clinical endpoint for EM treatment trials. However, as outlined above, pain alone does not fully capture the impact of EM/AM on patients' lives, nor the potential effectiveness/value of new treatments. This section proposes alternative endpoints that could be considered alongside (and, assuming regulatory changes, also alternatively to) pain, depending on the investigational drug and study design.

How could disease modification be measured as an endpoint in EM clinical trials:

Patient-reported outcome measures (PROMs) are increasingly recognized as important tools to capture the patient's perspective and experience with EM. PROMs can assess various dimensions like pain, quality of life, sexual function, and symptomatic impact that are relevant to disease modification. Specific validated PROM instruments for EM include the EM Health Profile (EHP-30), the EM Treatment Satisfaction Questionnaire (ETSQ), and the EM Symptom Diary (ESD).

Imaging techniques like TVUS and MRI can be used to quantify changes in EM lesion size, number, and location as potential endpoints for disease modification for OMA and DIE. However, there are currently no robust/accessible methods available to measure millimeter-scale changes in the size of individual lesions, nor overall lesion burden across multiple sites. Besides, lesion regression (while clearly desirable) may in itself not be an adequate endpoint from the patient's, regulator's or payer's perspective. It could, however, provide an important differentiation that may point towards a changing disease trajectory.

Biomarkers related to EM pathophysiology, such as inflammatory markers or markers of angiogenesis, could potentially be explored as surrogate endpoints for disease modification, but require further validation.

Endpoints related to **fertility**, namely implantation, pregnancy and live birth, are relevant for assessing disease modification in patients desiring to have children.

Table 4 further outlines potential endpoints and highlights whether these are already validated for use in clinical trials.

Endpoints	Description	Gaps
Qualitative: PROMs, PI-MBS, QoL	Key goal of EM treatment	Validated patient reported outcome Measures (PROMs)
Bleeding	Heavy/light	Established methodology in treatment of e.g. heavy menstrual bleeding or uterine fibroids
Fertility	Pregnancy, live birth	Timely measurement to confirm treatment success
Dysmenorrhea	Different types of pain keep patients from normal life	Dysmenorrhea and NMPP are assessed in EM trials, this leads to a selection of patients who present with both pain domains but leaves other EM patients underserved. For example, a patient with mainly dyspareunia may not be enrolled in a trial.
Non-Menstrual Pelvic Pain (NMPP)	Chronic Pain impacts QoL of patient	
Imaging for larger lesions	TVUS, MRI	Method to measure and monitor lesion size reduction
Imaging for smaller lesions	TVUS, MRI, SPECT	Method to detect (and measure) small lesions and their changes
Biomarkers	Several in development	Correlation with disease stage and activity to monitor effect of treatment
Surgical interventions	Select patients waiting for surgical treatment with the objective to delay the surgical intervention Measuring number of interventions/ avoidance of interventions over time	Standardized surgical intervention Objective measurement of treatment success

Table 4: Endpoint considerations

3.5 Comparators and Background Medication

The choice of comparator in clinical trials for EM drugs depends on several factors, including the patient population in question, the phase of the trial and the study objectives.

For proof-of-concept (Phase 2) trials, placebo is often a suitable choice as the primary aim is to assess the drug's efficacy and safety signals. Using placebo allows for a clear evaluation of the investigational drug's effects without the confounding influence of an active comparator.

However, for pivotal (Phase 3) trials aimed at regulatory approval, an active comparator representing the current standard of care is typically needed for reimbursement discussions. Placebo-controlled pivotal trials have been accepted for the last regulatory approvals in endometriosis, as no established second-line therapy for chronic treatment was available. This may change with the introduction of newer GnRH antagonists. Using an active comparator in pivotal trials is crucial for demonstrating the added therapeutic value of the new drug over existing treatments.

That said, the use of hormonal comparators and laparoscopic assessments present several challenges, including issues with blinding as their effects are often apparent to both patients and investigators, as well as concerns around cost, ethics, and surgeon intervariability in conducting and interpreting these assessments.

These factors can complicate the design and execution of pivotal trials for endometriosis therapies. Innovative trial designs and the use of alternative, non-invasive endpoints may be necessary to overcome these challenges and demonstrate the efficacy of new treatment options.

Ultimately, the choice of comparator has significant implications beyond efficacy and safety evaluations. An inappropriate comparator selection can hinder the ability to demonstrate the added therapeutic value of a new EM treatment, potentially leading to regulatory and reimbursement challenges.

It's important to note that in many EM trials, patients are allowed to continue their background pain medication, such as NSAIDs, to ensure ethical pain management. This practice, while necessary, can complicate the interpretation of efficacy results, particularly for pain endpoints. Other potential issues include contraception/fertility and drug interactions.

4 DEVELOPING TARGET PRODUCT PROFILES

A Target Product Profiles (TPP) summarizes the desired characteristics for a novel, yet-to-be-approved drug. It should primarily focus on patient needs but also must consider the perspectives of physicians, sponsors, regulators, and payers. The components of a TPP also need to be feasible in the context of drug discovery/development (cost/time/risk) and later real-world use.

Phase 1 and phase 2 trials will need to show preliminary safety and suggest relevant efficacy to help decide whether the drug candidate warrants advancement into phase 3 studies. For a phase 3 trial TPPs need to comply with regulatory requirements while achieving relevant data for a competitive and reimbursable product.

	EM: Existing Paradigm Hormonal drugs	EM: Disease-Modifying*	EM: Improving Fertility	AM
Positioning	2nd line treatment for patients not responding to standard of care (hormonal tx)	Patients not responding to hormonal treatments	Treatment alone or adjunct to assisted reproductive technologies	Non hormonal treatment
Standard of Care	combined oral contraceptives, progestagens, oral GnRH antagonists, laparoscopy	Laparoscopy	Laparoscopy, hormonal treatments that may interfere with fertility	Laparoscopic adenomyectomy/ GnRH agonists/ antagonists/ hysterectomy
PICO* patient population, intervention, comparison & outcomes		Depending on MoA select patients eg in inflammatory or fibrotic stage, dysmenorrhea or chronic pelvic pain	Patients with difficulties to get pregnant or implantation failure during IVF	Patients with AM
Rationale	Treating pain	Intervention to treat pain, prevent laparoscopy, disease progression and preserve or restore fertility	Prevent laparoscopy and enable or restore fertility	need to develop new drugs for treatment of AM
Intervention	Hormonal treatments, laparoscopy	Non hormonal disease-modifying drug	Non hormonal fertility-enhancing drug	Non hormonal AM treating drug
Background Medication	Analgesics	Analgesics, hormonal therapies?	Analgesics, alone or in addition to IVF cycle	Analgesics
Comparator for Phase III study	Placebo, SoC	Number of analgesics, delay to laparoscopy	Laparoscopy, Standard IVF treatment	Placebo or surgical management

	EM: Existing Paradigm Hormonal drugs	EM: Disease-Modifying*	EM: Improving Fertility	AM
1° Endpoint(s)	Pain reduction	Pain reduction Lesion size reduction Time to laparoscopy	Ovulation rate, pregnancy rate at 12 weeks, live birth rate	Pain reduction Lesion size reduction
Timing of 1° endpoint	3-6 months	3-12 months	12 weeks (pregnancy) 9 months (live birth)	6-12 months
Required effect size	Clinically meaningful improvement over comparator	Clinically meaningful improvement over comparator or baseline	Statistically significant improvement over comparator or baseline	Clinically meaningful improvement over comparator or baseline
Regulatory	Improve by 25% versus placebo	Define new endpoints clinically relevant for patients and validated for regulators	May qualify for expedited pathway if major advance?	Standard approval pathway
Market access	Differentiate from low-cost generics and SoC	Novel MoA. Work early with access specialists to collect necessary data to obtain reimbursement	Improved outcomes over existing fertility treatments. Cost saving by avoiding repeated IVF cycles	First approved medical therapy preventing invasive treatments
Pros	Known commercial positioning and regulatory pathway	Addresses unmet needs for patients underserved with today's treatments	Potential for premium pricing if live birth rate improves	Untapped market
Challenges	Reimbursement challenges	Powering study for multiple endpoints	Powering for low baseline live birth rate	No existing therapies for comparison?

Table 5: Summary of considerations for developing TPPs for selected high unmet need patient groups

Cross-disease perspectives: Endpoints (1)

The introduction of "patient-identified most bothersome symptom" (PI-MBS) in migraine creates a possible template for measuring clinical outcomes in a patient-focused way. PI-MBS showed to enhance the understanding of treatment benefits in migraine clinical trials beyond just looking at reduction in headache/ migraine days. The open-ended nature allowed capturing each patient's individualized most bothersome symptom.

Cross-disease perspectives: Endpoints (2)

The fields of rheumatoid and osteo-arthritis (as well as multiple sclerosis) developed from symptomatic to disease-modifying therapies, a move that required progress in both science (novel MoAs based on disease insights) as well as regulatory affairs (novel endpoints).

	EM (Non-Responders to Hormonal Treatments)	Patients with Fertility Issues	Patients with AM
Inclusion Criteria	– Confirmed EM diagnosis by laparoscopy or imaging – Inadequate response or intolerance to prior hormonal treatments	– Confirmed EM diagnosis – Trying to conceive for ≥1 year	– Confirmed AM diagnosis by imaging (or histology) – Symptomatic (e.g. heavy bleeding, pelvic pain)
Efficacy Endpoints	– Clinically meaningful reduction in pelvic pain scores – Improvement in quality of life – Reduction in lesion size/extent – Reduced need for surgical interventions (laparoscopies, hysterectomies)	– Increased pregnancy rates – Reduced time to pregnancy – Improved live birth rates	– Reduction in heavy menstrual bleeding – Reduction in pelvic pain scores – Improvement in quality of life – Reduced need for surgical interventions (laparoscopies, hysterectomies)
Safety	– Acceptable safety profile with minimal systemic side effects – No negative impact on fertility – No impact on Bone Mineral Density	– No teratogenic effects – Minimal impact on ovarian reserve	– Acceptable safety profile with minimal systemic side effects – No impact on fertility
Pricing	– Depending on the results premium pricing should be achievable	– Pricing aligned with other fertility treatment options	– Competitive pricing compared to surgical interventions – Potential for cost offsets by reducing bleeding/pain

Table 6: Basic Target Product Profiles for non-hormonal drugs to treat EM and AM

5 CONCLUSIONS AND NEXT STEPS

EM and AM have profound physical, psychological and social consequences interfering with patients' educational attainment, career advancement, and family planning aspirations. The diseases pervasive burden has been widely acknowledged, underscoring the urgent need to address these conditions that can strongly disrupt the lives of those affected.

Multi-stakeholder collaboration based on comprehensive datasets is required to drive changes in the requirements set forth by regulatory agencies and payers.

5.1 Key Objectives

- Real-World Data registries, better understanding of the natural history and the patients' needs
- Molecular understanding of the disease(s), yielding new MoAs and better patient segmentation
- Diagnostic methods to identify and stage the disease and monitor treatment effects
- Guidance for researchers: on endpoints, Dx, monitoring, PROMs etc
- Non-hormonal therapeutic showing lesion and pain reduction, prevention of new lesion growth

5.2 Key Areas for Action

The following table outlines key areas for action for various stakeholders involved in endometriosis research, treatment development, regulation, and patient care. This collaborative approach aims to accelerate progress in understanding the disease, developing targeted therapies, improving diagnostic tools, and enhancing patient care and support.

Stakeholder	Key Areas of Action
Researchers	– Reveal molecular pathogenesis and mechanisms of disease progression – Translate mechanistic insights into actionable strategies for prevention, early diagnosis, and targeted treatments of endometriosis – Develop improved preclinical models and increase the use of organoids and organ on a chip – Establish molecular criteria for patient stratification and targeted therapies – Standardize imaging criteria and classification systems – Validate advanced imaging techniques for early detection and monitoring
Startups	– Identify and validate clinical and imaging biomarkers for diagnosis, patient selection/stratification, measuring and monitoring lesion burden – Conduct robust target validation studies across multiple preclinical models – Engage with regulators early for scientific advice on development plan – Secure funding from investors based on strong preclinical data package, regulatory strategy
Industry	– Analyze clinical trial records of female participants to identify anecdotal effects of drugs on EM/AM symptoms and explore potential correlations with other diseases – Identify and validate potential therapeutic targets based on molecular understanding – Develop companion diagnostics based on molecular and imaging biomarkers – Incorporate standardized imaging criteria and biomarkers in clinical trials as endpoints – Conduct clinical trials using repurposed therapies based on novel insights into disease mechanisms – Early collaboration/interaction with start-ups to ensure they develop an optimal data package
Regulatory Bodies	– Incentivize new developments in EM/AM – Establish guidelines for molecular diagnostics, the use of imaging and targeted therapies in clinical trials in collaboration with patients and researchers – Support the development of non-hormonal disease-modifying therapies to enable the introduction of new treatments that offer long-term benefits for patients
Payers	– Assess cost-effectiveness of molecular profiling and targeted therapies – Review coverage policies for molecular and imaging diagnostic tests – Evaluate novel endpoints for coverage of targeted therapies – Align reimbursement/coverage with unmet need and impact of EM/AM
Patients/Advocacy Groups	– Contribute patient perspectives to research priorities and care standards – Raise awareness about needs for improved diagnosis, treatment, support and reimbursement

Table 7: Key Areas of Action

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7 GUIDELINES AND OTHER RESOURCES

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Figures have been created with BioRender.com

8 ACKNOWLEDGMENTS

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Disclaimer: The information, perspectives and recommendations expressed in this document resulted from a collaborative process coordinated by the Artemis Women's Health Foundation with the support of Catenion. They do not necessarily represent the views of every single individual mentioned above, nor of the organizations/companies they are affiliated with.

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9 ABBREVIATIONS

AM	Adenomyosis
rASRM	revised American Society for Reproductive Medicine
DIE	Deep Infiltrating Endometriosis
EM	Endometriosis
EU5	UK, Germany, France, Italy and Spain
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IVF	In-Vitro Fertilization
KOL	Key Opinion Leader
MoA	Mode of Action
MRI	Magnetic Resonance Imaging
NMPP	Non-Menstrual Pelvic Pain
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OMA	Ovarian Endometrioma
PICO	Patient Population, Intervention, Comparison & Outcomes
PROMs	Patient Reported Outcome Measures
PoC	Proof of Concept
SPE	Superficial Peritoneal Endometriosis
SPECT	Single-Photon Emission Computed Tomography
TVUS	Transvaginal Ultrasound
VC	Venture Capital

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