Paediatric inflammatory bowel disease: a multi-stakeholder perspective to improve development of drugs for children and adolescents

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Abstract

Background and Aims: Despite recent approvals for new drugs to treat adults with Crohn’s disease or ulcerative colitis, there are only two approved advanced treatment options (infliximab and adalimumab) for children with inflammatory bowel disease. There are many potential new therapies being developed for adult and paediatric inflammatory bowel disease. Moreover, regulatory agencies in both European Union and United States have processes in place to support the early planning and initiation of paediatric studies. Nevertheless, unacceptable delays in approvals for use of drugs in children persist, with an average seven-year gap, or longer, between authorisation of new inflammatory bowel disease drugs for adults and children.

Methods: A 2-day virtual meeting was held April 14–15, 2021 for multi-stakeholders (clinical academics, patient community, pharmaceutical companies, and regulators) to discuss their perspectives on paediatric drug development for inflammatory bowel disease.

Results: The multi-stakeholder group presented, discussed and proposed actions to achieve expediting the approval of new drugs in development for paediatric inflammatory bowel disease.

Conclusions: Collaborative action points for all stakeholders are required to make progress and facilitate new drug development for children with inflammatory bowel disease.

Keywords
Multi-stakeholder discussion; paediatric Crohn’s disease and ulcerative colitis, drug development
Introduction

The peak age of onset and diagnosis of inflammatory bowel disease occurs in people 15–29 years old but onset and recognition in younger children is becoming more common with the incidence of paediatric IBD (PIBD) increasing globally during the last few decades. Crohn’s disease (CD) in particular, may impede physical growth, pubertal development, and accrual of bone density. The relapsing nature of clinical symptoms in both CD and ulcerative colitis (UC) leads to missed days from school, and has a negative impact on psychological and social function. Despite recent approvals for new drugs to treat adult CD or UC, there are only two approved advanced treatment options for children with PIBD (infliximab and adalimumab, both anti-tumour necrosis factor [TNF] agents).

Pharmaceutical companies have a robust pipeline of potential new therapies and regulatory agencies in both EU and US require early planning for the initiation of paediatric studies. Nevertheless, unacceptable delays in development and subsequent approvals for use of drugs in children persist, with an average seven-year gap, or longer, between authorisation of new IBD drugs for adults and children. The key issues and barriers encountered in drug development for PIBD are well-recognised and have been previously described. To address these delays there continues to be a need for improvement of global collaboration among PIBD experts (clinicians, academics and researchers), the patient community, regulatory agencies and study sponsors (pharmaceutical companies).

conect4children (c4c) is a pan-European network that aims to facilitate the development of new therapies for children by facilitating the conduct of paediatric trials and promoting innovation and collaboration in paediatric drug development, including PIBD. conect4children is piloting the implementation of multi-stakeholder meetings to improve the development of new medicines for
children. A multi-stakeholder approach has previously been used to improve drug access in paediatric oncology through the ACCELERATE Pediatric Strategy Forums\(^{24}\). These forums allow important discussions and sharing knowledge between academics, regulatory agencies (FDA and EMA), industry, and the patient community (i.e., patients, patient representatives including family and carers, patient advocates and patient organisations). In addition, in paediatric oncology, these forums have promoted science-driven development strategies to address unmet needs and have facilitated prioritisation of compounds\(^{24}\). A 2-day virtual meeting was held April 14–15, 2021 for multi-stakeholders in PIBD to discuss how to facilitate expediting development of new drugs for children and adolescents with IBD. This article summarises the key points highlighted and action items identified by workshop participants, and is intended to promote innovative development pathways and strategies to increase accessibility of new medicines for all children and adolescents with PIBD.

**Materials and methods**

**Framework**

A multi-stakeholder approach utilised the conect4children’s network to provide a forum to discuss delays between adult and paediatric drug approvals for advanced drugs to treat IBD. Representatives of all key stakeholder groups were included in both the presentations and discussions (clinicians and academics, patient community, pharmaceutical companies, and regulators). During the 2-day meeting on the first day the background of the topics was set by members of the steering committee with perspectives from each stakeholder group, on the second day a summary of day 1 was presented with solutions presented in an open panel discussion with a resulting consensus and proposed strategy to go forward.

Issues discussed included:

- What it is like to be a teenager living with IBD
How drug development can be supported by working with:

- Networks and registries
- Increased extrapolation
- Other non-clinical trial evidence

Specific strategies for how to speed-up drug trials and approvals for PIBD.

While the funding and economic aspects of drug development and provision are important it was felt breadth of this subject and the very different payment/reimbursement processes in countries meant this could not be covered adequately and so was not part of the meeting.

Participants included those from academia (62 attendees), industry (35 from 11 pharmaceutical companies), regulators (25 including from United States Food and Drug Administration (FDA) and European Medicines Agency (EMA)), and the patient community (19). All participants provided informed consent that any views expressed during the meeting could be used in this article summarizing the meeting discussions.

Results

**Identified issues and hurdles from a multi-stakeholder perspective**

Issues and hurdles identified by various stakeholders have been previously well described (Figure 1). Stakeholders noted the time lag has been at least 7 years between marketing authorisation being granted for adult and paediatric indications for CD and UC. Despite 15 paediatric investigation plans approved by the EMA being in place for multiple classes of drugs which are being investigated for adult CD or UC, only two of these drugs are expected to have completed their paediatric trials in the next three years, and ten of these drugs do not yet have paediatric trials underway (Table 1). The time to primary completion date for clinical trials in PIBD is often many years after the start date and patient recruitment may be impacted by the presence of multiple competing drugs in development for PIBD. The ability to provide drugs off label varies widely by
country, in some it is quite quick and easy in others very difficult or not possible. Long delays in paediatric licensing after approval in adults encourages more off label use in children.

**Delays in paediatric trials**

The delay in completion of paediatric trials in IBD until long after adult drug approval results in the use of drugs in clinical practice that are not approved for children, without sufficient information to inform dosing or dose frequency. Recruitment of children and adolescents to clinical trials is often slow. The perceived lack of available subjects may be compounded by many patients being treated at relatively small centres, which do not always have the staff and resources to enrol their patients in clinical trials as funding for individual studies is often insufficient to sustain or employ enough staff.

In the United Kingdom, the Clinical Research Network (CRN) supports clinical trials and c4c also aims to support trial implementation by setting up resources to be shared between trials.

Academics highlighted that paediatric trials often start late after the drug is already on the market. This further reduces the pool of patients eligible for clinical trials as some may have already received the drug off-label, and indeed, the current guidelines for managing paediatric UC or CD recommend off-label use of drugs that are approved for adults. In practice guidelines recommend off label use of drugs in children after authors effectively extrapolate adult or non-trial data in children in the absence of regulatory trial data to achieve an approved pediatric indication.

**Regulatory Considerations**

Regulatory agencies have rigorous processes to review paediatric development plans proposed by sponsors (industry) and ensure the evidence generated by trials meet regulatory requirements and satisfactory standards. The EMA requires that all new applications for a paediatric investigation plan (PIP) should be submitted no later than the completion of the relevant pharmacokinetic (PK) studies
in adults. For the FDA the initial paediatric study plan (iPSP) must be submitted no later than 60 days after the date of the end-of-Phase 2 meeting. Paediatric development plans or a waiver must be in place in order for a new therapy to be eligible for marketing authorisation in an adult indication. Despite these efforts, delays in the initiation of paediatric studies frequently ensue, and can be related to many factors, including emerging adult safety or efficacy data resulting in the need to update or substantially change the paediatric plans. Moreover, academics and the patient community do not routinely provide feedback on proposed paediatric study protocols before the PSP or PIP negotiations are finalized. The ability to rapidly update PIPs when new data becomes available would be welcomed by pharmaceutical companies, and standardised consideration of views expressed by the patient community into PIPs would encourage greater input from this highly relevant stakeholder. Regulatory agencies have made efforts in recent years to develop better links with the patient community and integrate their views into the assessment processes, but there is the potential for further collaboration between industry sponsors and these patient organizations to further integrate the patient/parent perspective.

Although paediatric development plans must be in place within a specified timeframe, there are no fixed timings relative to adult approval for when paediatric clinical trials will be completed, although each paediatric plan has an agreed completion date often many years in the future. Factors which historically may have contributed to difficulties in enrolment and timely completion of PIBD trials include the previous requirement to include a placebo arm, trial procedures not felt by clinicians/investigators to be consistent with standard of care, and burden of trial participation to the patient community. Academics noted that they were less likely to discuss trial participation with the patient community if the trial comprised treatment arms that are not likely to benefit a patient who has already failed standard of care treatment. As such, there needs to be a potential benefit to all participating in a clinical trial and the trials need to be designed accordingly.
Currently, regulatory bodies recommend that children between 2 and 18 years be included in paediatric IBD trials. Workshop participants discussed that the prevalence of IBD in patients <6 years old and eligible for trials is lower than other age groups, in part because the onset of PIBD occurs more commonly in children >10 years of age; however, the incidence of PIBD in younger children is increasing. Adolescents usually receive the same dose as adults whereas there are examples where younger children of lower body weight may require relatively higher mg/kg dosing to achieve the same target exposure. Inclusion of a sufficient number of younger and lower bodyweight patients into clinical trials is critical, both to avoid future off-label use in the youngest patients, and to ensure adequate PK and pharmacodynamic (PD) information is generated to support paediatric dosing across the full spectrum of patients. Up to two-thirds of patients are underweight at diagnosis and one-third have impaired linear growth. Moreover, children with very early onset IBD (diagnosis <6 years) are likely to include 10–20% patients who have underlying primary immunodeficiencies (monogenetic disease), who would normally be excluded from PIBD trials after screening.

Although in many cases, regulatory agencies permit and encourage inclusion of adolescents 12–17 years old in adult trials, few industry sponsors have included adolescents in their adult trials for CD or UC thus far, which may be partly due to adult trials being placebo-controlled, and the desire to avoid placebo for adolescents who have already failed current standard of care treatment.

**Extrapolation**

Pharmaceutical companies and the academic community are well aligned on the importance of thoughtful use of data extrapolation from adult trials. Leveraging appropriate adult data to inform key elements of a PIBD programme is generally considered reasonable by regulatory agencies,
though the extent to which adult data can be relied upon, and the necessary gaps in knowledge that must be addressed will vary for each individual drug as well as drug class. Workshop participants emphasised the importance of utilizing PK and efficacy data from adults or older children/adolescents to inform dosing for young/lower-bodyweight children as one strategy to reduce the challenges in enrolment and promote timely collection of the necessary data to authorise a new drug in paediatric patients.

High burden of care placed on young people with PIBD and their families

It is important to understand the perspective and needs of young people with IBD, particularly as these groups of diseases can be invisible to outside observers. Members of the patient community spoke at the meeting to describe the impact of their illness on their lives (Table 2). People experience IBD in very individual ways and disease phenotype varies between patients. Furthermore, no drug is effective for or tolerated by all patients, emphasising the continued need to develop a variety of treatment options for an individualised treatment approach. Families with chronically ill children also suffer from the emotional burden of care, with high rates of dropping out of work, unemployment and work absenteeism among caregivers and parents. As such, the societal and economic costs for PIBD are high.

There remains a need to evaluate additional subcutaneous preparations of biologics used IV initially (subcutaneous dosing may be different in children to adults) plus novel oral preparations expeditiously in paediatric patients, to improve young people’s access to alternative methods of delivery and increased flexibility. Success in life for people with IBD relies on support from family, patient support groups and developing trusted relationships with healthcare professionals. New and
innovative treatments for PIBD are investments in these young people, to allow them to live full and productive lives without additional healthcare and social support.

Need to reduce the number of surgical interventions

Many patients require repeat surgical interventions because there is a lack of effective medical treatments and this is an indicator of more severe disease; approximately 20% of children with UC requiring a colectomy within childhood years and the cumulative incidence of surgery during the first 10 years after diagnosis of paediatric CD is between 15% and 35%. Published data indicate that anti-TNF are associated with a decreased risk of surgery and hospitalisation. Ideally, outcome measures for future therapies should thus include assessment of the drug’s ability to reduce the need for surgery.

Collaborative actions for accelerating development of new PIBD drugs through innovative clinical trial programmes

Suggestions were made by stakeholders to optimise and accelerate the development of new PIBD drugs, although further discussions are needed to achieve this vision (Box 1). All workshop participants agreed that they wished to reduce the time between approval of new drugs in adults and children.
Box 1: Actions for accelerating development of new drugs for PIBD

1. Implement innovative trial designs for children with IBD early in a clinical development program.

2. Start PIBD trials earlier for new drugs in development before marketing authorisation in adults, ideally on completion of phase 2 studies with sufficient evidence of clinical benefit and safety in adults.

3. Prioritise evaluation in the paediatric population of novel compounds that meet patients’ needs, including providing alternate mechanisms of action and multiple routes of administration.

4. Encourage concurrent evaluation of adolescents (12 to 17 years) with Phase 3 adult trials in UC and CD, when scientifically justified.

5. Generate high-quality data in adults with adequate dose-ranging in order to support relevant and meaningful extrapolation of pharmacokinetic and efficacy data from adult trials to children.

6. Design PIBD clinical trials to maximise appropriate extrapolation of efficacy data from adults, including aligning key design features and endpoints between the adult and paediatric programmes, and use of resolution of inflammation on endoscopy as key efficacy endpoint.

7. Promote high-quality and systematic collection of data for inclusion in registries to further support our understanding of the safety of new drugs after their introduction to market.

8. Avoid parameters likely to lead to unsuccessful trials (i.e., elements that place undue
There was considerable discussion regarding the need for adequate PK assessment in younger children, especially those of lower body weight. There was recognition among stakeholders that it may not always be feasible to collect sufficient data for children <6 years old prior to marketing authorisation for older children or adults, meaning that provisions for trials in younger children may have to take place after regulatory approval for older paediatric patients.

Stakeholders agreed further work would require to form a dedicated multi-stakeholder consensus group to discuss extrapolation of data, how to design appropriate clinical trials in order to collect enough good-quality evidence in adults and adolescents that can be leveraged to inform the necessary data in younger/smaller children and calculating study sample sizes based on the data required to make robust extrapolations (see Box 2).

**Expanding and adapting the current clinical research framework**

**Network of professionals**

There are a number of networks working in the field of PIBD (with individual academics often being members of more than one), however there is currently no formalised link with regard to trials in PIBD. Collaborations tend to occur on an ad hoc basis driven by the academics involved. An example...
of this was the PIBDNet sponsored PIBD SETQuality Study collaborating with CIDSCann to share the Canadian PIBD database.

PIBD-Network (PIBD-Net), is an international group of academics and physicians intended to create a transparent infrastructure to advance the care of children with IBD through investigator- and industry-initiated research. Other communities of healthcare professionals and industry researchers includes groups such as the European Crohn’s and Colitis Organisation (ECCO) including a paediatric focused committee (paediatric ECCO; P-ECCO), the Paediatric IBD Porto group within European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), Canadian Children IBD Network (CIDsCANN) and ImproveCareNow. In planning the meeting invitations were sent out through these networks and members attended the meeting.

**Paediatric IBD registries**

Although paediatric registries for IBD exist, they are usually used for post-marketing drug safety surveillance. For example, the Children’s Registry for the Advancement of Therapeutics (CREATE™) IBD Registry, working with ImproveCareNow, aims to facilitate collaboration between multiple industry sponsors to advance the development of safety monitoring registries. Paediatric registry data can also be used to supplement clinical trial data in order to aid clinical decisions, such as monitoring long-term remission rates (including corticosteroid-free remission), surgery, hospitalisations, flares and reasons for stopping or switching treatment due to an adverse event or loss of response. Registries include PIBD-NET sponsored study to observe the disease course of paediatric-onset IBD and response/non-response to therapies (PIBD-SETQuality inception cohort). There is also the PIBD-SETQuality safety study which is recording rare and severe complications in patients with PIBD across a very large population of patients. Registries already help predict the...
complicated disease course for children with newly diagnosed Crohn’s disease.\textsuperscript{40} and can provide data to further extrapolation, as long as collected in a structured, standardised way and complies with regulatory requirements.\textsuperscript{41} Other registries which include or are exclusive to PIBD include industry led post marketing studies (Cape, Abbvie) and non-industry led regional, national or international studies (UK (UK IBD Registry), Germany (CEDATA-GPGE), USA (Pediatric RISK stratification study), Canada (CIDsCANN) and Northern France (EPIMAD)).

\textit{Patient networks}

Patient groups for IBD are located across Europe, United States, Australia and many other countries, including the European Patients’ Forum (EPF), EURORDIS-Rare Diseases Europe and European Federation of Crohn’s and Ulcerative colitis Association (EFCCA).

\textit{Committed patient community}

The stakeholders recognised that despite the increased interest and the existence of frameworks and practical recommendations, more can still be done to engage further with the patient community.\textsuperscript{42} Committed patients are ready to engage much more with researchers, healthcare professionals, regulators, health technology assessment (HTA) bodies and competent bodies on pricing and reimbursement (‘payers’) to improve their own health and medical care. They are also willing to provide their perspective on research prioritisation (e.g., helping to define unmet needs), clinical trial design and patient information provided by sponsors during recruitment, as well as early dialogue with regulators pre-approval and with HTA bodies and payers post-approval. As such, all documents, including study results, should be presented in plain language to facilitate non-specialist engagement.
Regulatory issues identified

There are opportunities for increased alignment between regulatory agencies on topics including novel endpoints, better guidance on what data extrapolation would be sufficient for a drug approval in children, and use of real-world evidence for monitoring adverse events. There is also a need for harmonisation of iPSPs for the FDA and PIPs for the EMA. To improve transparency, the EMA makes public high-level information on each PIP. The FDA currently does not publish similar information in a public forum. Detailed publication of both PIP and PSP at time of approval would be a first step towards being informed about the level of alignment between the EMA and FDA requirements for PIBD trials. Increased transparency could promote learning and collaboration among various stakeholders involved in conduct of paediatric IBD clinical trials.

Building on the current regulatory framework

Currently, the FDA, EMA, Therapeutics Goods Administration (TGA, Australia), Pharmaceuticals and Medical Devices Agency (PMDA, Japan), and Health Canada discuss submitted select paediatric plans during regularly scheduled cluster meetings, and there has been a proposal for sponsors to submit simultaneously to regulatory agencies to facilitate discussion among regulators and global alignment, similar to drug development for new cancer treatments for children.\(^4^3\) Indeed, the FDA and EMA have provided a common commentary concerning commonly requested topics with regards to paediatric oncology development plans\(^4^4\) By addressing the key issues jointly, the agencies have provided a forum for streamlined assessments of PIPs/iPSPs for new paediatric oncology drugs and allows for early coordination of global paediatric drug development plans.\(^4^5\) A similar process for new drugs for PIBD would help foster shared responsibility between regulatory agencies, industry sponsors and trial investigators for new drug development programmes for PIBD.
Prioritisation of new advanced drugs

Currently there is no prioritisation of pipeline drugs in terms of enrolment into clinical trials. If pipeline drugs were prioritised, the drug(s) with highest priority would potentially have rapid completion of the clinical trial programme(s) to determine safety and efficacy. There was discussion that the current approach to study each pipeline drug individually may not be best serving the paediatric patient population, and stakeholders are interested in further discussion of strategic prioritisation and lifecycle management of paediatric plans within each class of compounds. It is essential that multi-stakeholder prioritisation discussions take place, especially for those with the same or similar mechanisms of action. Academics and the patient community input should be sought; however, the current regulatory requirements for pharmaceutical companies to study children with IBD for all new medicines in development for adults with IBD must also be taken into consideration.

Strategic recommendations

The high-level strategy for expediting new drug development for paediatric patients with IBD was proposed by meeting participants (Box 2).

Box 2. Next steps

1. A dedicated international multi-stakeholder core group should be set up to coordinate actions required to accelerate access to new drugs for children with IBD.

2. An international multi-stakeholder working group should further discuss appropriate use of extrapolation from adult data in PIBD in order to improve efficiency and feasibility of timely completion of studies.

3. A multi-stakeholder working group should explore how to prioritise different classes of investigational drugs.
Discussion

Despite many efforts from all stakeholders there has been little progress in reducing the time from initiation to completion of PIBD trials over the last 10 years. As there are now many new classes of drugs being developed for adults with IBD, there is a risk that this delay will continue, or even worsen. Although specific stakeholders have documented their individual perspectives on delayed access, it is now time to join forces and work on collaborative action points to make progress and facilitate new drug development for children. The Institute for Advanced Clinical Trials for Children (I-ACT) and conect4children’s joint taskforces within the PIBD global community are working to engage with multiple stakeholders across industry, academia, regulatory agencies and the patient community in order to promote continued progress in the field, including setting up working groups for the patient community, and discussions on extrapolation, prioritisation of within-class drug development and real-world data/evidence and clinical trial designs.
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Data availability statement

No new data were generated or analysed in support of this article. All data are derived from sources in the public domain.

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Declaration of interests

AMG: Consultant to Abbvie, Amgen, BristolMyersSquibb, Janssen, Lilly, Merck, Pfizer. Speaker fees from Abbvie, Janssen, Nestle. Investigator-initiated research support from Abbvie.

CP: Is an employee of the European Medicines Agency.
FMR: Collaboration (advisory boards, consulting, scientific presentations) with Schering-Plough, Ferring, MSD, Johnson & Johnson, Centocor, AbbVie; Nestlé Nutrition Institute, Nestlé Health Science, Danone, MeadJohnson; Takeda, Celgene, Biogen, Bristol Myers Squibb, Gossamer, Lilly

DT: during last three years, has received consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, AbbVie, Takeda, Atlantic Health, Shire, Celgene, Lilly, Roche, ThermoFisher, and Bristol-Meyers Squibb.

GV: Provided advice on paediatric oncology drug development to Astra-Zeneca, Bayer, Bristol Meyers Squib, Celgene, Hutchinson-Medi Pharma, Ipsen, Celltrion, Merck, Novartis, Pfizer, Roche/Genentech. He does not accept personal remuneration. GV is also is a board member of SIOP Europe (the European Society for Paediatric Oncology).

JSH: Advisory board for Janssen, AbbVie. Consultant to Lilly, Boehringer Ingelheim, Bristol Myers Squibb, Thetis, Takeda, Pfizer.

KC: Is an employee of Janssen, UK.

KN: Is an employee of the European Medicines Agency.

LdR: Collaboration (such as involved in industry sponsored studies, investigator-initiated study, consultancy) with Celltrion, AbbVie, Eli Lilly, Takeda and Pfizer.

AE, FL, IL, MC-B, MG, ZG,: None.

NMC: Trial funding, advisory board and speakers fees paid to his institution from AbbVie, Eli Lilly, Takeda, Shire, Pfizer and Janssen.

RN: Is an employee of Johnson & Johnson.

TAA: Is an employee of the US Food and Drugs Administration.

WC: Is an employee of Eli Lilly and Company.
As well as the authors declaration of interests, participants of the 2-day meeting included employees of AbbVie, AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, GSK, Janssen, Johnson & Johnson, OSE Immunoth, Pfizer, Roche Genentech and Servier.

**Author contributions**

All authors have made substantial contributions to all of the following: (1) the conception and design, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. In addition, GV was responsible for the conception of the multi-stakeholder meeting; meeting content and agenda (programme committee members) were LdR, GV, NC, MC, MG, CP, TA, KN, KC, RN, WC, JSH, FR; all authors took part in panel discussion; first draft manuscript development was by LdR, GV and NC.
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Figure legends

Figure 1. Issues leading to delayed paediatric approvals of innovative drugs being developed for adults with IBD
Table 1. Paediatric clinical trial status for advanced drugs with EMA paediatric investigation plans

<table>
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<tr>
<th>Drug name</th>
<th>Mode of action</th>
<th>Disease</th>
<th>Year of adult indication approval* or expected date of completion of ongoing Phase 3 trials</th>
<th>Year of paediatric indication approval* or expected date of completion of ongoing Phase 3 trials</th>
<th>PIP completion date</th>
<th>Delay in paediatric approval</th>
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<td><strong>Approved for both adult and paediatric CD/UC indications</strong></td>
<td></td>
<td></td>
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<td>Infliximab</td>
<td>Anti-TNFα</td>
<td>CD/UC</td>
<td>Approved for adult CD/UC in 1998/2005</td>
<td>Approved for paediatric CD/UC in 2006/2011</td>
<td>Complete</td>
<td>8 years for CD; 6 years for UC</td>
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<td>Anti-TNFα</td>
<td>CD/UC</td>
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<td>Approved for paediatric CD/UC in 2014/2021</td>
<td>Complete</td>
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<td>Golimumab</td>
<td>Anti-TNFα</td>
<td>UC</td>
<td>Approved for CD in 2013</td>
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<td>2024</td>
<td>At least 9 years</td>
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<td>Anti-a4-b7 integrin</td>
<td>CD/UC</td>
<td>Approved for CD/UC in 2014</td>
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<td>UC</td>
<td>Approved for UC in 2018</td>
<td>Paediatric UC primary completion date Q3 2026</td>
<td>2026</td>
<td>At least 8 years</td>
</tr>
<tr>
<td><strong>Drugs with ongoing adult and paediatric CD/UC trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Type</td>
<td>Indications</td>
<td>Primary Completion Date of CD/UC Trials</td>
<td>Pediatric UC Primary Completion Date</td>
<td>Year of Approval</td>
<td>Approval Status</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------------------</td>
<td>-------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Mirikizumab</td>
<td>Anti-IL-23</td>
<td>CD/UC</td>
<td>Primary completion expected Q4 2023/Q3 2025**</td>
<td>Paediatric UC primary completion date Q3, 2027</td>
<td>2027</td>
<td>Unknown</td>
</tr>
<tr>
<td>Etrolizumab</td>
<td>Anti a4-b7/aE-b7 integrin</td>
<td>CD/UC</td>
<td>Primary completion of CD trials expected Q3 2021; inconsistent results for UC</td>
<td>No registered paediatric trials</td>
<td>2024</td>
<td>Unknown</td>
</tr>
<tr>
<td>Etrasimod</td>
<td>S1P1,4,5 modulator</td>
<td>CD/UC</td>
<td>Primary completion date of CD/UC† trials expected Q4 2021</td>
<td>No registered paediatric trials†</td>
<td>2025</td>
<td>Unknown</td>
</tr>
<tr>
<td>Filgotinib</td>
<td>JAK1 inhibitor</td>
<td>CD/UC</td>
<td>Filed a request to EMA for marketing authorisation in 2020 for UC Primary completion date for CD expected Q4 2022</td>
<td>No registered paediatric trials</td>
<td>2026</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gusekumab</td>
<td>Anti-IL-23</td>
<td>CD</td>
<td>Primary completion of CD/UC trials expected Q2 2022</td>
<td>No registered paediatric trials</td>
<td>2026</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ozanimod</td>
<td>S1P receptor agonist</td>
<td>UC</td>
<td>Primary completion date of CD†/UC expected 2023/2022</td>
<td>No registered paediatric trials†</td>
<td>2026</td>
<td>Unknown</td>
</tr>
<tr>
<td>Risankizumab</td>
<td>Anti-IL-23</td>
<td>CD/UC</td>
<td>Primary endpoint met in Phase 3 trials in CD; Primary completion of UC trials expected Q3 2022†</td>
<td>No registered paediatric trials†</td>
<td>2026</td>
<td>Unknown</td>
</tr>
<tr>
<td>Brazikumab</td>
<td>Anti-IL-23</td>
<td>CD/UC</td>
<td>Primary completion of CD trial</td>
<td>No registered paediatric trials§</td>
<td>2030</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Primary completion of CD/UC trials expected Q4 2023/Q3 2025**

††Primary completion of UC trials expected Q4 2021

†††Primary completion of CD trials expected Q3 2021; inconsistent results for UC

‡‡Primary completion date of CD/UC expected 2023/2022

§§Primary completion of CD trial

Drugs with adult ongoing CD/UC trials and approved PIP for CD/UC but no paediatric trials registered
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>Disease(s)</th>
<th>Primary Completion Dates</th>
<th>Pediatric Trials</th>
<th>Approval Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upadacitinib</td>
<td>JAK1 inhibitor</td>
<td>CD/UC</td>
<td>Primary completion of CD/UC† trials (Q3 2021/Q1 2021)</td>
<td>No registered paediatric trials†</td>
<td>2028</td>
<td>Unknown</td>
</tr>
<tr>
<td>TD-1473</td>
<td>Pan-JAK inhibitor</td>
<td>UC</td>
<td>Primary complete of UC trials expected (Q2 2025; CD phase 2 trial ongoing)</td>
<td>No registered paediatric trials</td>
<td>2030</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ravagalimab</td>
<td>Anti-CD40</td>
<td>UC</td>
<td>Phase 2 trial primary completion date (Q4 2021)</td>
<td>No registered paediatric trials</td>
<td>2034</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Drugs with adult approval and/or ongoing CD/UC trials but with no PIP for CD/UC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mode of Action</th>
<th>Disease(s)</th>
<th>Approval for use in adults with CD in the United States¶</th>
<th>No ongoing registered paediatric trials</th>
<th>Approval Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab</td>
<td>Anti-TNF</td>
<td>CD</td>
<td>Approved for use in adults with CD in the United States¶</td>
<td>No ongoing registered paediatric trials. Previous paediatric CD trials terminated</td>
<td>2008</td>
<td>Unknown</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Selective adhesion molecule inhibitor</td>
<td>CD</td>
<td>Approved for use in adults with CD in the United States¶</td>
<td>No ongoing registered paediatric trials</td>
<td>2008</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Primary completion dates of trials collated from clinicaltrials.gov, December 2021.

*Year of approval is for either FDA or EMA marketing authorisation;

**Patients 15–80 years old are eligible for inclusion in mirikizumab Crohn’s disease trials;

†Patients 16–80 years old are eligible for inclusion in UC trials for etrasimod, risankizumab29 and upadacitinib;
‡Patients 12-75 years old are eligible for inclusion in CD trials for ozanimod;

¶The FDA does not currently publish initial paediatric study plans (iPSPs). Certolizumab and natalizumab do not have EMA approval for treating either adult CD or UC.

CD, Crohn’s disease; CD40, cluster of differentiation 40; EMA, European Medicines Agency; IL, JAK, Janus kinase; interleukin; PIP, paediatric investigation plan; S1P1,4,5, sphingosine 1-phosphate receptor 1,4,5; UC, ulcerative colitis
Table 2. Living with paediatric IBD

<table>
<thead>
<tr>
<th>Burden of disease</th>
<th>Burden of care/disease management</th>
<th>Life challenges and constraints on daily activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complexity of diagnosis</strong></td>
<td><strong>Time consuming self-management even when feeling well</strong></td>
<td><strong>Limitations on physical, social and education activities</strong></td>
</tr>
<tr>
<td>• Potential long delay between onset of symptoms and a confirmed diagnosis</td>
<td>• Early responsibility for own health</td>
<td>• Frustration when unable to keep up with peers</td>
</tr>
<tr>
<td>o Some doctors doubt symptoms described by parents/carers and the young person</td>
<td>• Competence taking complex daily medication regimens</td>
<td>• Missed school days</td>
</tr>
<tr>
<td>prior to diagnosis</td>
<td>• Scheduling/re-scheduling infusions around education needs such as national examinations to avoid academic failure</td>
<td>• Need to find inner strength to develop resilience and determination to overcome challenges and achieve personal goals</td>
</tr>
<tr>
<td>• Unmanaged symptoms can be severe enough to require emergency hospital admission</td>
<td></td>
<td>• Disadvantaged when accessing work/employment market</td>
</tr>
<tr>
<td>• Risk of serious comorbid inflammatory conditions</td>
<td></td>
<td>• Difficulties in establishing personal relationships and setting up their own families in early adulthood</td>
</tr>
<tr>
<td><strong>Physical complaints/symptoms</strong></td>
<td><strong>Attending frequent medical appointments across multiple specialties and healthcare professionals</strong></td>
<td>• Lack of flexibility of infusion clinics potentially limit choice of work/education placements if travel costs to ‘home’ clinic are prohibitive</td>
</tr>
<tr>
<td>• Diarrhoea/ urgency to use toilet</td>
<td>• Rheumatologist for joint problems</td>
<td><strong>Lack of understanding from peers</strong></td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>• Dietitian</td>
<td>• IBD symptoms can be a source of ridicule despite talking about their illness. For example:</td>
</tr>
<tr>
<td>• Painful joints</td>
<td>• Mental health worker for chronic stress</td>
<td></td>
</tr>
<tr>
<td>• Chronic fatigue</td>
<td>• Vaccine specialist who understands how their immunosuppressive drugs will affect immunisation</td>
<td></td>
</tr>
<tr>
<td>• Perianal (fistulising) disease</td>
<td>• Regular intravenous infusions at specific healthcare</td>
<td></td>
</tr>
<tr>
<td>Facilities</td>
<td>Families, parents/carers</td>
<td>A young person’s need for frequent bathroom visits</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>• Frequent hospitalisations, including for surgery</td>
<td>• Scheduling appointments around parent/carer work schedules and activities of other family members (work absenteeism)</td>
<td>• An inability to exercise due to pain</td>
</tr>
<tr>
<td>• Pharmacy visits to collect medication</td>
<td>• Emotional, physical and financial support required for the young person with IBD</td>
<td>• Weight gain due to steroids</td>
</tr>
</tbody>
</table>

- Extremely embarrassing and stressful, especially among adolescents
- Frequent hospitalisations, including for surgery
- Pharmacy visits to collect medication
- Scheduling appointments around parent/carer work schedules and activities of other family members (work absenteeism)
- Emotional, physical and financial support required for the young person with IBD
- A young person’s need for frequent bathroom visits
- An inability to exercise due to pain
- Weight gain due to steroids
Figure 1.

Children should be able to access new drugs that safely and effectively treat IBD

Drivers
- High patient burden of disease
- Limited approved treatment choices
- Extensive pipeline treatments for adult IBD
- Similar disease pathology in adults and children
- Extensive regulatory requirements for paediatric trials
- Patients, parents and care-givers support and expect new drug development

Barriers
- Insufficient global alignment
- Delayed start of paediatric development
- Off-label use of adult-approved drugs
- Trial participation burden
- Slow recruitment

No access to innovative drugs in a timely manner