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A *FLT3-ITD* mutation drives progression and may lead to lower patient survival.[1-3]

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Prescribing information for: XOSPATA™ ▼ 40 mg film coated tablets (gilteritinib). **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. **Posology and administration:** Treatment with gilteritinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. See *Special warnings and precautions for use* section on tests to be conducted prior to initiation e.g. blood chemistries, ECG & pregnancy test. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response (patient did not achieve a composite complete remission (CRc) after 4 weeks of treatment), the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT), Planned HSCT: Interrupt treatment one week prior to administration of the conditioning regimen for HSCT. Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc. Elderly: No dose adjustment is required in patients ≥65 years of age. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment. Please refer to SPC, section 4.2 for full instructions for use in hepatic & renal impairment. Paediatric population: The safety and efficacy of gilteritinib in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to $5HT_{2B}$, there is a potential impact on cardiac development in patients less than 6 months of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use:** Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended. Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec.The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF interval returns to within 30 msec of baseline or ≤480 msec. Patients with QTcF interval increase by >30 msec on day 8 of cycle 1 should have a further ECG on day 9; if QTcF increase is confirmed gilteritinib dose should be reduced to 80 mg. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation. Pancreatitis: There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved. Toxicity: If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). Interactions: Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A,P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib. Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient. Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib. **Interactions:** Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. See Special Warnings and Precautions for Use section above for further information on this and the effects of gilteritinib on products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. *Gilteritinib as an inhibitor or inducer:* gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin). **Fertility, pregnancy and lactation:** Pregnancy: Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. Breastfeeding: Breastfeeding should be discontinued during treatment with gilteritinib and for at least two months after the last dose. Fertility: There are no data on the effect of gilteritinib on human fertility. **List of adverse reactions:** *Prescribers should consult the SPC for full information on adverse events* **List of adverse reactions:** Very common (≥1/10): Dizziness, Hypotension, Cough, Dyspnoea, Diarrhoea, Nausea, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood alkaline phosphatase increased, Pain in extremity, Arthralgia, Myalgia, Fatigue, Peripheral oedema and Asthenia. Common (≥1/100 to <1/10): Anaphylactic reaction, Electrocardiogram QT prolonged, Pericardial effusion, Pericarditis, Cardiac failure, Differentiation syndrome, Musculoskeletal pain, Acute kidney injury and Malaise. Serious adverse reactions: The most frequent serious adverse reactions noted from evaluation of 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib were acute kidney injury, diarrhoea, ALT increased, dyspnea, AST increased and hypotension. Other clinically significant serious adverse reactions included differentiation syndrome, electrocardiogram QT prolonged and posterior reversible encephalopathy syndrome. **Overdose:** There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours. **Cost (excluding VAT):** United Kingdom (UK): XOSPATA 40 mg film-coated tablets x 84: £14,188.00. **Legal classification:** POM. **Marketing authorisation number:** Great Britain (GB): PLGB 00166/0425. Northern Ireland NI: EU/1/19/1399/001. **Marketing authorisation holder:** GB: Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX. NI: Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands. **Date of preparation:** March 2023. **Document number:** MAT_UK_XOS_2023_00039. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication.

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bjh research paper

Qualitative study to support the content validity of the immune thrombocytopenia (ITP) Life Quality Index (ILQI)

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Summary

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder. Bleeding is the primary symptom that presents in varying severities. ITP has a negative impact on health-related quality of life (HRQoL). The ITP Life Quality Index (ILQI) was developed as a 10-item patient-reported outcome measure to assess impact on HRQoL in ITP. The objective of the present study was to confirm the content validity of the ILQI with a qualitative interview study in the UK involving 15 adult participants with ITP. Combined concept elicitation (CE) and cognitive debriefing (CD) interviews were conducted to explore the symptoms and impacts associated with ITP and confirm content validity of the draft ILQI. The CE phase elicited 14 ITP symptom concepts, including: bruising (all 15 patients, 100%), fatigue (14, 93·3%) and bleeding gums/blood blisters (13, 86·7%). Impacts included decreased ability to participate in sport (all 15 patients, 100%) and anxiety (12, 80%). The CD phase resulted in an adjustment to the ILQI recall period from 1 week to 'the past month'. Updates were made to improve relevance and response options. The qualitative interviews support the content validity of the ILQI and confirm that the concepts assessed are relevant and consistently understood and interpreted by adult patients with ITP.

Keywords: qualitative, Immune thrombocytopenia, HRQoL, content validity, ILQI.

Introduction

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterised by isolated thrombocytopenia defined as a peripheral blood platelet count of $<100 \times 10^9$/l.[1] ITP is considered a rare disease, diagnosed primarily by excluding other causes of thrombocytopenia. ITP is caused by immunological destruction of otherwise normal platelets and impairment of platelet production, most commonly occurring in response to an unknown stimulus. ITP may occur in isolation (primary ITP) or in association with other disorders (secondary ITP). Recent data suggest that the incidence in adults is approximately equal in both sexes, except in the mid-adult years (20–30 years of age), when the disease is more prevalent in women.[2,3] The UK incidence of adult ITP is estimated to be ~120/year and 3000–3500 people are affected at any one time in England and Wales.[4]

Bleeding is the primary symptom experienced by patients with ITP. However, bleeding can present in various severities from mild bruising and mucosal bleeding to severe haemorrhage.[5] Symptoms of ITP can lead to negative impacts on a

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patient's daily life.[2,6] Fatigue, as well as fear of bleeding[7] may cause interference with the ability to work, resulting in emotional and financial impacts.[6,8] While the significant impact of ITP on patient's health-related quality of life (HRQoL) has been recognised, there is little qualitative evidence reporting the patient experience of ITP within the published literature.[7–10]

Clinical assessment of ITP severity often focusses on platelet count and risk of bleeding, yet ITP is known to impact the patient's HRQoL and fatigue.[6] Patients with ITP who do not bleed with low platelet counts or have sufficient counts to prevent frequent bleeding may still experience significantly impaired HRQoL due to factors such as altered body image or fear of bleeding.[7] Despite the significant impairments experienced by the patient, existing tools designed to assess HRQoL in individuals with ITP are lengthy and therefore difficult for use in clinical practice.[8] Consequently, a draft patient-reported outcome (PRO) questionnaire, the ITP Life Quality Index (ILQI) was developed to assess the impact of ITP on patients and aid discussion between patients and physicians and inform treatment decisions. The ILQI was initially developed by clinical experts in the field of ITP and the format of the items and response options was based on the Dermatology Quality of Life Index (DLQI).[11] Although the ILQI was developed based on this existing, well-established questionnaire, no patients were involved in the development of the instrument, as it was initially only intended to be used as a draft measure and introduced into clinical practice for pilot testing. However, it was soon acknowledged that there was an unmet need to assess HRQoL in patients with ITP and therefore, a more rigorous process was required to ensure the ILQI was developed according to best practice guidelines. Consequently, interviews with adult patients with ITP were proposed to confirm the content validity of the questionnaire.

The aim of the present study was to conduct qualitative patient interviews to confirm the content validity and refine the initial version of ILQI for inclusion in an international online survey.[9,10] The interviews aimed to qualitatively explore the concepts relevant to patients with ITP, to ensure that the ILQI includes all concepts relevant to patients with ITP, and that these concepts are asked in a way that is understandable and are interpreted consistently by patients with ITP.

Methods

Before conducting the patient interviews, a brief literature review was conducted to gain an understanding of the disease experience of adult patients with ITP, specifically the symptoms, impacts and treatments, and used to inform the content of the interviews. To supplement the literature search, information was also collected from three ITP-specific online patient forums/blogs, which gave insights from adult patients living with ITP. The review of published literature led to the identification of key ITP symptoms including fatigue, bleeding, bruising, menstrual symptoms, nerve pain and feeling generally unwell. ITP impacts identified included physical impacts, impacts on daily activities, emotional impact, impact on work/education, social impact and impact on reproductive health. These findings were used to inform the development of a draft conceptual model and to inform the content of the interview guide. The conceptual model was then updated iteratively to include both the findings from the literature review and the findings from the patient interviews, to provide a visual representation of the ITP disease experience, derived from multiple sources (Fig 1).

The literature review was followed by a qualitative interview study with 15 adult patients with ITP recruited from

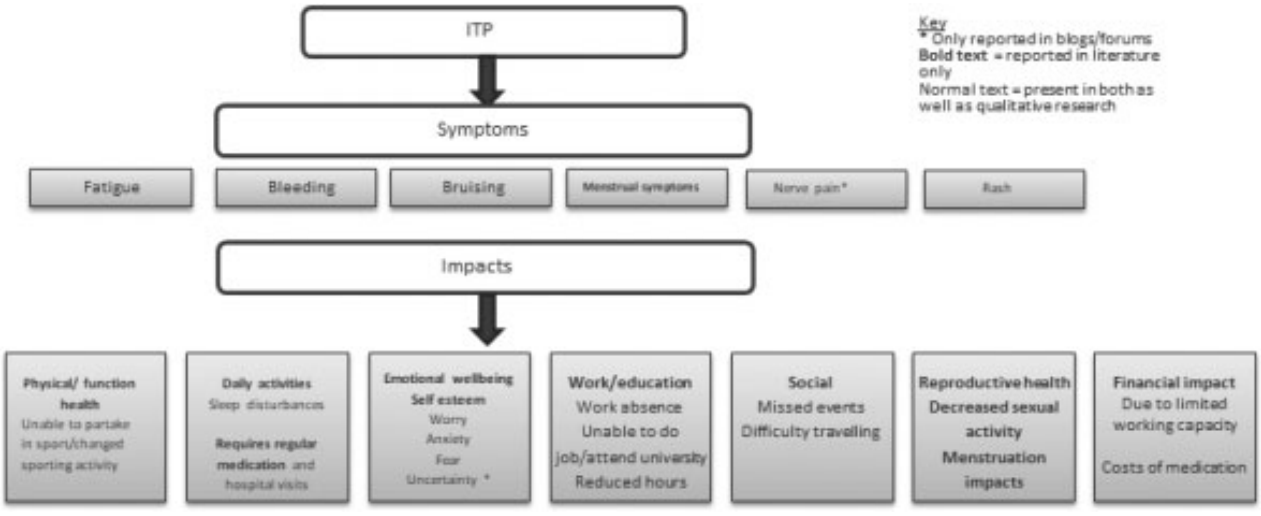

Fig 1. Conceptual model of the immune thrombocytopenia (ITP) disease experience.

the UK. Interviews were conducted via telephone and lasted ~60 min, with both concept elicitation and cognitive debriefing portions. The interviews aimed to explore the symptoms associated with ITP to gain an in-depth understanding of the ITP disease experience and impacts associated with ITP to confirm the content validity of the ILQI. Interviews were conducted over two rounds, with 11 patients in the first round and four patients in the second round, to allow for interim analysis and any adaptations to the interview guide or ILQI where needed based on patient responses. A sample of 15 patients was considered sufficient for conceptual saturation. Ethics approval was obtained from an independent ethics board, Salus Institutional Review Board (approval code NO8027A) and all patients provided written informed consent before participating in the interview. Before the interviews, patients were sent the ILQI via post or e-mail for reference during the interviews.

The ILQI is intended for use in adult patients with ITP across a range of disease severity levels. Therefore, to be eligible for the study participants were aged ≥18 years, diagnosed with ITP, able to read and speak fluently in the English language and have access to a telephone. Quotas were used to ensure patients were recruited with a range of demographic and clinical characteristics. Participants were recruited from the UK ITP Support Association via an advertisement that interested participants had to actively respond to on a voluntary basis. Potential participants were provided with information outlining the study requirements. To ensure protection of personal data participants were assigned a unique identification (ID) number to ensure confidentiality; the ID number included current age of patient-gender-age at diagnosis, e.g. 73-F-65.

All interviews were conducted by trained qualitative interviewers using a semi-structured interview guide. During the concept elicitation phase of the interview, participants were asked a series of broad, open-ended questions designed to elicit information regarding one the symptoms, two the impacts and three the treatments experienced as a result of their ITP. Questions were designed not to lead participants in their responses and allow participants the opportunity to mention symptoms spontaneously. Following this, participants were asked more focussed questions designed to probe on concepts that they may not have mentioned during the interview, such as how ITP affected participants emotionally and socially. This ensured that all study objectives were met, and all study questions were answered, thus identifying the concepts that are most important to patients and the language patients used when talking about these concepts.

During the cognitive debriefing phase of the interview, participants were asked to complete the draft ILQI, using a 'think-aloud' exercise that involved the participants speaking aloud their thoughts as they read the instructions and each item and selected a response for each item. Participants were asked detailed questions regarding their understanding and relevance of each item, instruction and response options. Participants were also asked to comment on the wording of the ILQI and suggest alternative wording and to assess whether any key concepts were missing from the instrument, or any concepts were redundant.

All interviews were audio-recorded and transcribed verbatim for the purposes of analysis. Qualitative analysis was conducted using Atlas.ti software.[12] Transcripts were assessed, coded and analysed by two researchers to ensure consistency. Thematic analysis methods were used, whereby sections of the transcripts for individual participants (i.e. quotes) were assigned codes reflective of the underlying concepts.[13–15] A coding scheme was developed based on the topics discussed in the interview guide with codes assigned to each interview transcript differentiating between spontaneously elicited concepts (i.e. those concepts that the patient mentioned during the open-ended discussion) and concepts discussed only when probed (i.e. those concepts that the patient reported to be important but only when asked directly by the interviewer). The interview findings were assessed for confirmation of conceptual saturation.

Results

Of the 15 participants interviewed, most were female (10) and the sample had a mean (range) age of 51·3 (23–73) years and most were White Caucasian (14) (Table I). Participants had a range of educational levels, with just over half (eight) having an undergraduate or bachelor's degree. Most of the participants were working full or part time at the time of their involvement in the study (nine) and were in 'Good' general health (eight; according to a single item assessing general health). Participants received their ITP diagnosis at an mean (range) age of 40·9 (21–70) years, the mean disease duration was 10 years, and for the majority it took several months to receive a diagnosis (nine). Participants expressed a range of views in terms of how easy it was for them to receive their diagnosis of ITP.

Concept elicitation results

Symptoms. From the concept elicitation phase of the interviews a total of 13 symptom concepts were elicited including bruising (15 patients, 100%), fatigue (14, 93·3%) and bleeding from gums/blood blisters (13, 86·7%). Supplementary Table SI presents an overview of the six most reported symptoms, along with illustrative quotes. Other symptoms reported by one patient each included: brain bleed, eye bleed, broken blood vessels, blood clots, extreme pain, migraine and stomach upset. The symptoms of nerve pain and feeling unwell were identified from the review of patient blogs and published literature respectively but were not confirmed by participants in the qualitative interviews.

The concept elicitation phase of the interview also elicited several different impacts reported by individuals with ITP. The most reported impacts included decreased or total lack

Table I. Overview of demographic and clinical characteristics.

Demographic and clinical characteristics	Value
Number of particpants	15
Sex, *n* (%)	
Female	10 (66·7)
Male	5 (33·3)
Age, years	
Mean (range)	51 (23–73)
Median	59
<30 years, *n*	3
30–39 years, *n*	2
40–49 years, *n*	1
50–59 years, *n*	2
60–69 years, *n*	5
>70 years, *n*	2
Highest level of education, *n* (%)	
Did not complete high school	1 (6·7)
Completed high school/secondary school	3 (20)
Completed further education/college	1 (6·7)
Undergraduate or bachelor's degree	8 (53·3)
Postgraduate degree	2 (13·3)
Work status, *n* (%)	
Working full or part time	9 (60)
Retired	4 (26·7)
Not working due to ITP	2 (13·3)
Race, *n* (%)	
White Caucasian	14 (93·3)
Asian	1 (6·7)
General health, *n* (%)	
Excellent	1 (6·7)
Good	8 (53·3)
Fair	5 (33·3)
Poor	1 (6·7)
Age at ITP diagnosis, years	
Mean (range)	41 (21–70)
Median	37
Disease duration, years	
Mean (range)	10 (1–38)
Median	9
Diagnosed <5 years	6
Diagnosed 5–10 years	5
Diagnosed >10 years	4
Time to receive diagnosis, *n* (%)	
Days	3 (20)
Weeks	3 (20)
Months	9 (60)
How easy was it to receive a diagnosis? *n*, (%)	
Very easy	4 (26·7)
Somewhat easy	5 (33·3)
Neither easy nor difficult	1 (6·7)
Somewhat difficult	3 (20)
Very difficult	2 (13·3)

of ability to participate in sport (15 patients, 100%), anxiety (12, 80%) and having to avoid non-sporting activities (11, 73·3%). A summary of the impacts reported during the interviews and the most frequently reported aspect of each impact, with illustrative patient quotes are presented in Supplementary Table SII.

The evidence elicited from the literature review, including review of patient forums/blogs, and concept elicitation phase of the interviews was used to develop a conceptual model of the ITP disease experience (Fig 1).

Cognitive debriefing results

When analysing the cognitive debriefing part of the interview, codes were developed to assess the patient level of understanding and relevance of each item of the ILQI. Participants were asked to report any changes they would make to the ILQI items to improve clarity and asked if they thought anything was missing or whether they felt any items were not relevant to their ITP disease experience.

All participants (15, 100%) confirmed their understanding of the ILQI instructions and added that the clear instructions enabled them to complete the ILQI independently. The draft ILQI had a recall period of 1 week, 13 participants (86·7%) reported that a recall period of 1 week was not appropriate, as their ITP disease experience did not change on a weekly basis or that they did not participate in the activities listed in the ILQI on a weekly basis. Following this feedback, the recall period for the ILQI was increased to 'the past month'.

> 'For me personally, it would be – it would make more sense if it was over the period of a month.' (64-M-62)

The response options included in the draft ILQI were: 'Never', 'Sometimes', 'More than half the time' and 'All the time'. A total of 10 (66·7%) participants found the draft response options appropriate, while five (33·5%) suggested making a change to the response options. Suggested changes included: changing to a '0–10 numeric rating scale' for all items, changing 'more than half the time' to 'half the time' and removing 'more than half the time' completely. However, all participants were able to use the existing response options to select an appropriate response and thus they were retained without changes. The final four interviews confirmed that participants were able to understand and use the response options to select an appropriate response.

> '"More than half the time" maybe I would just change, because "never", "sometimes", and "all the time" is fine, but "more than half the time", I can't see that that works, really…I think just "never", "sometimes", or "all the time", because those are the three options.' (59-F-32)

The level of understanding and perceived relevance associated with each item on the draft ILQI is presented in Table II, along with recommendations for rewording of the items and the proposed updated item wording.

After analysis of the qualitative interviews, the results were presented to a steering committee which included ITP clinical experts (three) as well as ITP patient representatives (two). The steering committee made a number of suggestions

Table II. Item tracking matrix.

Original ILQI item	Level of understanding (n = 15)	Relevance (n = 15)	Reword suggestions	Updated item
1. How often has ITP impacted on your working life? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'Going to work outside the home. I never think of working life as being in the home. Working life is actually earning'* (62-F-51)	**9/15 (60%)** *'Well, I had to give up work. I mean, you know, eventually it was all the time'* (73-F-35)	Add a 'not applicable' response option: *'If there was a box that said "not applicable", that might be better than "never".'* (73-F-70) Make the item and response options relevant to patients who are studying as well as working	How often has ITP impacted on your working life or studies? Never, sometimes, more than half of the time, all of the time, I am not currently working/studying
2. How often has your ITP impacted your ability to concentrate on everyday tasks? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'you know, concentrating on the computer, writing emails or putting in spreadsheets'* (56-M-46)	**12/15 (80%)** *'I don't think I can concentrate like I used to.'* (66-M-56)	No reword suggestions, no changes	How often has your ITP impacted your ability to concentrate on everyday tasks? Never, sometimes, more than half of the time, all of the time
3. How often has your ITP impacted your social life? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'Going out, going to the pub, going whatever people do'* (62-F-51)	**13/15 (86·7%)** *'I would say probably more than half the time just because I have had to limit the number of things I can do.'* (73-F-70)	No reword suggestions, no changes	How often has your ITP impacted your social life? Never, sometimes, more than half of the time, all of the time
4. How often has your ITP impacted your sex life? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'it would not impact my sex life if I had a long-term relationship, because they would understand . . .But if – if I was going out there with somebody new, I'd be – I'd be very, very concerned if there was a time when I had a lot of bruising'* (60-F-37)	**7/15 (46·7%)** *'Sometimes you don't have the energy to participate in that sort of thing.'* (56-M-46)	Add a 'not applicable/prefer not to say' option	How often has your ITP impacted your sex life? Never, sometimes, more than half of the time, all of the time, not applicable/prefer not to say
5. How often has your ITP impacted your energy levels? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'How easy it is to do things, whether I get tired or not'* (62-F-51)	**14/15 (93·3%)** *'Pretty much all. As I've explained in the past I do get – I do get very tired, certainly at the end of the day'* (56-M-46)	No reword suggestions, no changes	How often has your ITP impacted your energy levels? Never, sometimes, more than half of the time, all of the time

Table II. (*Continued*)

Original ILQI item	Level of understanding (n = 15)	Relevance (n = 15)	Reword suggestions	Updated item
6. How often does ITP impact your ability to undertake everyday tasks such as brushing your teeth, getting dressed? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'And my answer is, yes. And so ultimately, brushing teeth is actually a psycho -- it has its psychological elements. So, sometimes -- and I know this sounds ridiculous, but I brush my teeth in the dark'* (47-F-37)	**4/15 (26·7%)** *'I'd say more than half the time, because obviously sometimes you want to brush the teeth and not spit out and find blood in your sputum'* (56-M-46) *'I wouldn't say that's part of ITP. I might be quite wrong, but from my perspective, it's not something that it affects'* (73-F-70)	Eleven participants did not find this item relevant to their ITP experience and two participants suggested removing this item The item was changed to assess more general activities of daily living with the example activities removed.	How often has ITP impacted your ability to undertake daily tasks? Never, sometimes, more than half of the time, all of the time
7. How often has your ITP impacted your ability to care for loved ones? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'I probably would say partners, children, probably grandchildren'* (73-F-70)	**7/15 (46·7%)** *'that is very appropriate because that does have a massive affect, because my husband has been ill for a very long time, and that, um, I have had to limit, and he's aware, but you know there's sometimes I can't even go into hospital'* (73-F-70)	Five participants reported that they did not currently 'care for loved ones' The wording was changed to 'support others' to make the item relevant to more people	How often has your ITP impacted your ability to support others? Never, sometimes, more than half of the time, all of the time
8. How often do you take days off work or education because of your ITP? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'In the last week I haven't cancelled a work appointment because of my ITP. Sometimes I've cancelled a whole week.'* (47-F-37)	**8/15 (53·3%)** *I put sometimes because obviously if I had a client, they wanted to make an appointment to see me, and it -- it comes on a day when I'm actually going to have my treatment, then I can't do that'* (64-M-62)	Move this item to Q2 in the ILQI so it followed the other item about the impact of ITP on work The response option was updated to include those in education (e.g. I am not currently working/studying)	How often do you take days off work or education because of your ITP? Never, sometimes, more than half of the time, all of the time, I am not currently working/studying
9. How often does your ITP negatively impact your hobbies or ability to play sport? Never, sometimes, more than half of the time, all of the time	**15/15 (100%)** *'Negatively means, you know, you just couldn't do it. It would be too dangerous'* (59-F-32)	**13/15 (86·7%)** *'I'm aware of my ITP. I don't tend to ride the motorbike when I know it's very low'* (64-M-62) *'it never has for me. . .I don't do sport and my hobbies are gentle'* (62-F-51)	The word 'sport' was removed from the item to focus the item on hobbies (which could still include sport if that was a relevant hobby for the patient)	How often does your ITP negatively impact your hobbies? Never, sometimes, more than half of the time, all of the time
10. How often does your ITP negatively impact your normal capacity to exercise? Never, sometimes, more than half of the time, all of the time	**14/15 (93·3%)** *Simply because I always want to exercise, it's just about the length of it and also it's the vigorousness'* (47-F-37) *'that is a difficult one because I don't know what it means, 'your normal capacity to exercise'* (62-F-51)	**12/15 (80%)** *'I get so tired I can't walk far'* (62-F-51) *'Never, because I'm not the sort of person that does much exercise and what I do – cycling, aqua-aerobics – is fine. So, never really for me'* (59-F-32)	No reword suggestion, no changes	How often does your ITP negatively impact your normal capacity to exercise? Never, sometimes, more than half of the time, all of the time

for further updates to the instrument including the use of past tense language throughout the ILQI, adding an additional response option of 'I am not currently working/studying due to other reasons' being added to items 1 (impact on your working life) and 2 (impact on your ability to concentrate on everyday tasks), changing the wording of item 7 to 'undertaking of daily tasks' and rewording item 8 to 'ability to support people close to you'.

After these updates a final version of the ILQI was created for inclusion in a multi-country, cross-sectional survey: the ITP World Impact Survey (I-WISh).[9,10,16] This ILQI version contained 10 items asking patients to report the impact of their ITP on their HRQoL over the past month.

Discussion

The aim of the present study was to elicit qualitative insights into the patient experience of ITP, understand the impact ITP has on patient's HRQoL, and confirm the content validity of the ILQI. The results of the qualitative interviews provided in-depth insights into the patient experience of ITP, allowing a gap in the current published literature to be addressed. The information gained from the present study allowed the patient perspective of living with ITP to be thoroughly explored and the symptoms and impacts that are considered most important to patients to be confirmed, leading to further understanding of the ITP disease experience. This evidence supports the content validity of the ILQI and confirms that the concepts assessed in the ILQI are relevant to patients and patients consistently understood the ILQI items. This research also contributes to further understanding the ITP disease experience from the patient perspective.

While the patient feedback largely supported the content of the draft ILQI, with participants confirming the relevance of the concepts assessed by the ILQI, certain aspects of the instrument were updated to ensure it is fully patient-centric and reflects the patient experience. Such updates included extending the recall period from 1 week to 1 month and adding 'not applicable' options to certain items. While guidance for the development of PRO instruments suggests shorter recall periods are preferable to avoid recall bias,[17] it also states that they should be appropriate for the condition of interest. It is for this reason that the recall period for the ILQI was extended to 1 month as participants reported that 1 week would not be a sufficient length of time to see any changes in their ITP symptoms and thus the impacts these have on their HRQoL. The wording of two items [Item 6 (impact on everyday tasks) and Item 7 (impact on caring for loved ones)] was also updated to more accurately reflect the patient experience to ensure the version of the ILQI that resulted from the qualitative interviews was as patient-centric as possible. The item asking about the impact on sex life was reported to be less relevant than other items, possibly due to the personal nature of the concept, and subsequently, a 'not applicable/prefer not to say' response option was added to reduce the potential for missing data. While participants in this qualitative interview study found the impact on sex life to be a less relevant impact, literature suggests that patients with ITP experience a negative impact on sexual activities, including reduced libido and bruising and bleeding during intercourse,[18] therefore it was retained as an important concept to assess in the ILQI with the additional response option. While participants in the interviews did also report concepts such as emotional impacts and impacts on sleep, these concepts were not included in the ILQI, due to being considered more distal concepts and to prevent the ILQI from becoming too long and burdensome for patients. Even without the addition of these concepts, participants in the interviews felt the ILQI sufficiently assessed their ITP disease experience.

Currently there is a lack of awareness of the full impact of ITP on patients, leading to inconsistency of routine care of patients with ITP. It is hoped that adoption of the ILQI in routine care will improve consistency of patient-centric decision-making, leading to better outcomes for all patients and particularly those without bleeding who experience a high degree of morbidity.

While the present study has many strengths, such as gaining direct patient input on the experience of living with ITP and the contents of the ILQI, there are limitations that should be acknowledged. While considered an appropriate sample size for a qualitative research study,[19] all patients were in the UK and the majority were White Caucasian with a mean age of 51 years, suggesting that there was a lack of diversity in the sample and there needs to be caution when applying these findings to the general ITP population. Also, all patients were recruited from a patient support association and volunteered to participate, which could suggest they are more knowledgeable about ITP than other patients and could have a greater severity of disease experience than others. These factors may suggest that the sample is not representative of the general ITP population. To enable the work to be generalised to a wider population, future validation studies should include participants from across a geographical spectrum, from different countries and cultures. While participants were recruited via the UK ITP Support Association, specific clinician-confirmed diagnosis was not sought prior to their study participation. Again, future studies would benefit from this additional level of disease confirmation and data relating to treatments received. It should also be acknowledged that the participants had a relatively high education level (66·6% had a degree and only one patient did not complete high school), which is not necessarily representative of the general population seen in clinic. Also, future studies would benefit from having a large sample size in round two, for the testing of the changes made to the items. In this sample, most participants understood all items, regardless of education level. It should also be noted that current testing of the ILQI has been limited to paper versions of the instrument, therefore, further testing would be required to support the use of any future electronic or digital versions of the questionnaire.

While patient input is a key aspect of the PRO development process, it is also acknowledged that it would be beneficial to obtain feedback from clinicians in terms of how the ILQI can be implemented in clinical practice and the potential benefits of this.

The content validity of the ILQI has been explored via the conduct of a review of published literature and patient forums, and blog and qualitative interviews with individuals with ITP. As a next step it will be important to assess the psychometric properties of the instrument. The ILQI was included in a multicountry cross-sectional survey (I-WISh), where the psychometric properties of the instrument and the severity of HRQoL impairment in this population will be reported. The psychometric properties of the ILQI have been confirmed using data from the I-WISh data and the English version of the ILQI has both content validity and psychometric validity and is an appropriate PRO to be used in clinical practice.

The present study contributes to the understanding of the patient experience of ITP, specifically the impact it has on a patient's HRQoL. This valuable insight not only led to a better understanding of the ITP disease experience, but also the further development of the ILQI as a tool for monitoring ITP and the impact it has on patients in routine clinical practice. It is hoped that cross-cultural implementation of the ILQI will lead to more consistency of treatment in clinical practice and better outcomes for patients with ITP.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Symptoms of immune thrombocytopenia (ITP) and supporting patient quotes.

Table SII. Impacts of immune thrombocytopenia (ITP) and supporting patient quotes.

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