Mission:Cure

# Exploration of Flares as an Endpoint in Clinical Trials

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**Subject**: Use of flares as an endpoint in chronic pancreatitis clinical trials and analogous diseases.

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Flares, severe episodic exacerbations of symptoms, represent one of the most disruptive aspects of chronic pancreatitis (CP). Although chronic and recurrent acute pancreatitis (RAP) have lacked validated endpoints for regulatory approval, flares are emerging as reliable, patient-relevant, and measurable outcomes. They reflect real-world clinical burden, drive healthcare utilization, and are increasingly accepted by regulators in adjacent diseases. The purpose of this memo is to present information that could support using flares as primary or secondary endpoints in CP and RAP trials.

**I. Regulatory Precedent: Flares in Pancreatitis and Related Conditions**

Since December 2024, flares have been used as primary or secondary clinical trial endpoints in the regulatory approval of two therapies for conditions involving pancreatitis.

1. Inebilizumab (Amgen) for IgG4-related disease (RD)
    - IgG4-RD causes inflammation and fibrosis of various organs, including the pancreas. When it occurs in the pancreas, it is known as Type 1 autoimmune pancreatitis (AIP).[1]
    - **Primary endpoint:** Time to disease flare, defined as the time in days from Day 1 (dosing) to the date of the first treated.[2]

[1] Zhang, L., & Smyrk, T. C. (2010). Autoimmune pancreatitis and IgG4-related systemic diseases. *International Journal of Clinical and Experimental Pathology*, *3*(5), 491–504.

[2] Amgen. (2025). *A Phase 3, Randomized, Double-blind, Multicenter, Placebo Controlled Study of Inebilizumab Efficacy and Safety in IgG4-Related Disease* (Clinical Trial Registration NCT04540497). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT04540497

- **Definition of flare**: New or worsening clinical features of IgG4-related disease that met organ-specific flare criteria and for which there was no clear alternative diagnosis.[3]
    - Based on Events Identified During the 52-Week Randomized Controlled Period (RCP) that met organ-specific flare criteria and prompted treatment (e.g., increased glucocorticoids or immunotherapy).
    - Reported whenever they occurred, as soon as the investigator deemed treatment necessary.
- **How flares were determined:** Flare criteria (symptoms, physical examination, imaging, laboratory and pathological findings) were developed for the trial by a multinational panel of experts on IgG4-related disease.[4]
- **List of criteria for flares**[5]
    - 3 categories were used to describe aspects of disease activity: “Organ/Site Score”, “Symptomatic”, and “Urgent”.
    - Organ/Site Score: Manifestations of disease were given a score from 0 (normal or resolved) to 4 (worsened despite treatment) based on the overall level of IgG4-RD activity in that organ.
    - Symptomatic: Is the disease manifestation in a particular organ system symptomatic? (Yes or No). Symptoms need to be specified if yes.
    - Urgent: Does the disease in this organ/site require treatment immediately to prevent serious organ dysfunction? (Yes or No).
- **List of criteria for pancreas-specific flares**[6]
    - Required to be present if patient has prior history of IgG4-related autoimmune pancreatitis
        - New or worsening symptom and/or physical exam (PE) finding and new or worsening lab finding consistent with flare of pancreas/common bile duct
        - Or imaging or endoscopy confirming new or worsening involvement
    - Required to be present if patient has no prior history of IgG4-related autoimmune pancreatitis:
        - New symptom, PE finding, and/or lab finding consistent with involvement

[3] Amgen. (2025). *A Phase 3, Randomized, Double-blind, Multicenter, Placebo Controlled Study of Inebilizumab Efficacy and Safety in IgG4-Related Disease* (Clinical Trial Registration NCT04540497). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT04540497

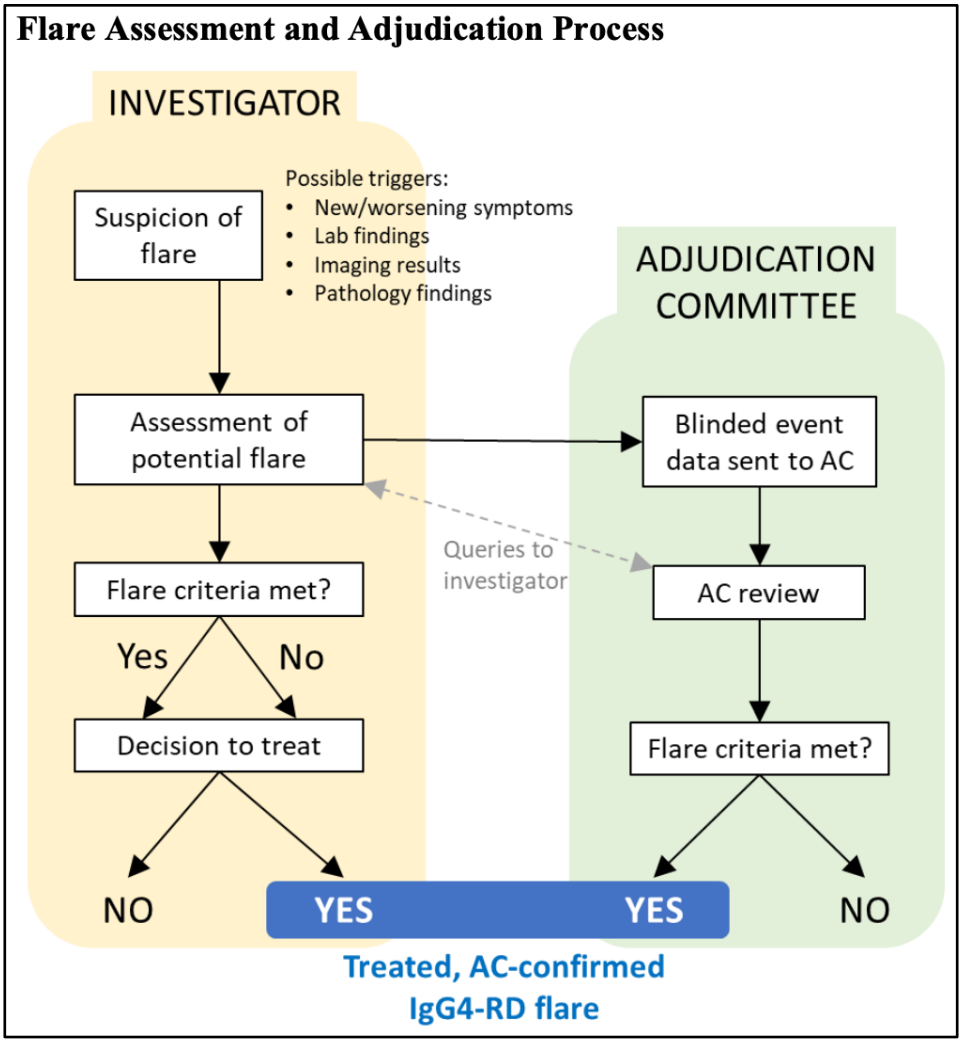
[4] Stone, J. H., Khosroshahi, A., Zhang, W., Torre, E. D., Okazaki, K., Tanaka, Y., Löhr, J. M., Schleinitz, N., Dong, L., Umehara, H., Lanzillotta, M., Wallace, Z. S., Ebbo, M., Webster, G. J., Valle, F. M., Nayar, M. K., Perugino, C. A., Rebours, V., Dong, X., … Culver, E. L. (2025). Inebilizumab for Treatment of IgG4-Related Disease. *New England Journal of Medicine*, *392*(12), 1168–1177. https://doi.org/10.1056/NEJMoa2409712

[5] Ibid.

[6] Ibid.

        - And either new imaging or endoscopy confirming involvement, or biopsy confirming pancreatic involvement
    - Required to be absent:
        - Alternative diagnosis or inconsistent biopsy findings
- All potential flares were evaluated by a central expert adjudication committee, composed of physicians experienced in the care of patients with IgG4-RD.

Figure 1: Diagram outlining the assessment and adjudication process for suspected flares.[7]




* AC = Adjudication committee; IgG4-RD = immunoglobulin G4-related disease.

[7] Stone, J. H., Khosroshahi, A., Zhang, W., Torre, E. D., Okazaki, K., Tanaka, Y., Löhr, J. M., Schleinitz, N., Dong, L., Umehara, H., Lanzillotta, M., Wallace, Z. S., Ebbo, M., Webster, G. J., Valle, F. M., Nayar, M. K., Perugino, C. A., Rebours, V., Dong, X., … Culver, E. L. (2025). Inebilizumab for Treatment of IgG4-Related Disease. *New England Journal of Medicine*, *392*(12), 1168–1177. https://doi.org/10.1056/NEJMoa2409712

2. Olezarsen (Ionis) for Familial Chylomicronemia Syndrome (FCS)
    - Familial Chylomicronemia Syndrome (FCS) is a rare autosomal genetic condition caused by mutations of the lipoprotein lipase gene, resulting in elevated triglycerides and chylomicrons in the blood plasma.[8] Extremely high triglyceride levels can cause acute pancreatitis.[9] Repeated acute pancreatitis events can, over time, lead to CP.[10]
    - **Secondary endpoint:** Adjudicated acute pancreatitis event rates over the 12-month treatment period.[11]
        - Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Participant-Years During the Treatment Period in Participants With Prior History of Pancreatitis and in Participants with No History of Pancreatitis
        - *All adverse events that consistently occurred during the study with an event of acute pancreatitis were adjudicated by a blinded, independent committee according to the Atlanta classification of acute pancreatitis. These events were categorized as 1) documented pancreatitis, 2) probable pancreatitis, 3) possible pancreatitis, 4) unable to adjudicate and 5) no diagnosis of acute pancreatitis. The adjudicated event rate represents the average number of events per 100 participant-years during the treatment period.
    - **Definition of flare**: 2012 Atlanta classification definition of acute pancreatitis.[12]
        - To diagnose an acute flare of pancreatitis, 2 of the following 3 criteria must be met:
            I. Abdominal Pain (presence)
                - Sudden-onset, severe pain in the upper abdomen
                - Often radiates to the back
                - Typically persistent and disabling

            II. Elevated Pancreatic Enzymes
                - Blood lipase or amylase ≥3× the upper normal limit

[8] Regmi, M., & Rehman, A. (2025). Familial Hyperchylomicronemia Syndrome. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK551655/

[9] *Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases—ScienceDirect*. (n.d.). Retrieved July 17, 2025, from https://www-sciencedirect-com.revproxy.brown.edu/science/article/pii/S1424390320301265

[10] Gagyi, E.-B., Teutsch, B., Veres, D. S., Pálinkás, D., Vörhendi, N., Ocskay, K., Márta, K., Hegyi, P. J., Hegyi, P., & Erőss, B. (2024). Incidence of recurrent and chronic pancreatitis after acute pancreatitis: A systematic review and meta-analysis. *Therapeutic Advances in Gastroenterology*, *17*, 17562848241255303. https://doi.org/10.1177/17562848241255303

[11] Ionis Pharmaceuticals, Inc. (2025). *A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)* (Clinical Trial Registration NCT04568434). https://clinicaltrials.gov/study/NCT04568434

[12] Sarr, M. G. (2013). 2012 revision of the Atlanta classification of acute pancreatitis. *Polskie Archiwum Medycyny Wewnetrznej*, *123*(3), 118–124. https://doi.org/10.20452/pamw.1627

- Note: Lipase and amylase levels may be normal or mildly elevated lipase during chronic pancreatitis flares, limiting their reliability as standalone diagnostic markers

III. Imaging Findings

- CT scan, MRI, or ultrasound shows signs consistent with acute pancreatitis
- Examples: pancreatic swelling, fluid collections, necrosis

- **How flares were determined in the trial:**
  - A blinded, independent adjudication committee used the Revised Atlanta Classification to evaluate reported adverse events. Each event underwent central review to determine if it met diagnostic criteria for acute pancreatitis based on symptoms, enzyme levels, and imaging.[13]
  - The Atlanta classification categorizes acute pancreatitis into three severity levels: mild, moderately severe, or severe. Mild acute pancreatitis lacks organ failure and local or systemic complications. Moderately severe pancreatitis involves transient organ failure (resolving within 48 hours), local complications, or exacerbation of co-morbid disease. Severe pancreatitis is characterized by persistent organ failure (lasting longer than 48 hours).[14]

3. <u>In progress: ARO-APOC3 / Plozasiran (Arrowhead) for FCS</u>
   - This investigational RNA interference (RNAi) therapeutic aims to reduce the level of APOC3 thus reducing triglycerides and restoring lipids to more normal levels, reducing pancreatitis events.[15]
   - **Secondary endpoint:** Number of participants with positively adjudicated events of acute pancreatitis from the first dose of study drug through Month 12 (randomized period) and through month 36 (open-label period where both researchers and participants are aware which treatment is being administered).[16]
   - **Definition of flare**: Revised Atlanta Classification from 2012.
     - Adjudication was conducted using the Revised Atlanta Classification, and results were reported as event rates across treatment arms.[17]

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[13] Ionis Pharmaceuticals, Inc. (2025). *A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)* (Clinical Trial Registration NCT04568434). https://clinicaltrials.gov/study/NCT04568434

[14] Sarr, M. G. (2013). 2012 revision of the Atlanta classification of acute pancreatitis. *Polskie Archiwum Medycyny Wewnetrznej*, *123*(3), 118–124. https://doi.org/10.20452/pamw.1627

[15] Watts, G. F., Rosenson, R. S., Hegele, R. A., Goldberg, I. J., Gallo, A., Mertens, A., Baass, A., Zhou, R., Muhsin, M., Hellawell, J., Leeper, N. J., Gaudet, D., & PALISADE Study Group. (2025). Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. *The New England Journal of Medicine*, *392*(2), 127–137. https://doi.org/10.1056/NEJMoa2409368

[16] Ibid.

[17] Ibid.

These examples demonstrate that the FDA has accepted flare events as both primary and secondary endpoints in contexts directly relevant to pancreatitis.

**II. Flares as Endpoints in Analogous Chronic Diseases**

Several chronic, episodic diseases with similar symptom unpredictability and pain-centric presentations have used flares as clinically meaningful endpoints.

1. Inflammatory Bowel Disease (IBD): Ulcerative Colitis & Crohn's disease.
    - Both IBD and chronic pancreatitis are chronic GI diseases marked by recurrent flares that cause significant pain, functional disruption, and healthcare use**.**
    - **Flares** are understood as worsening of symptoms from a baseline state
        - "... an increase in an individual's gastrointestinal and extraintestinal burden of symptoms, which combined may be ascribed to an increase in their overall IBD activity."[18]
    - The FDA guidance for clinical trial endpoints for Ulcerative Colitis specifies what outcome measures should be prioritized.
        - The "ideal primary efficacy assessment tool used in clinical trials to support marketing approval for the treatment of UC would consist of the following scales: 1) A signs and symptoms assessment scale, best measured by a **patient-reported outcome instrument** (or, in the case of young children (5 to 6 years old) or those unable to provide valid and reliable self-report, an observer-reported outcome instrument; 2) An endoscopic and histological assessment scale, best measured by a clinician-reported outcome instrument."[19]
    - Clinical trials often aim to reduce both the severity and frequency of flares, a core treatment goal shared with chronic pancreatitis.[20]
        - Flares (or rather lack of) are usually used as **secondary endpoints**, with clinical / endoscopic remission as primary endpoints.
        - **Endpoints**: Time to flare, flare rate.
    - E.g. CELEST Phase 2b trial of Upadacitinib (ABT-494) in Crohn's disease.[21]

[18] Witges, K., Sexton, K., Graff, L. A., Targownik, L. E., Lix, L. M., Haviva, C., Stone, J., Shafer, L. A., Vagianos, K., & Bernstein, C. N. (2021). What Is a Flare? The Manitoba Living With IBD Study. *Inflammatory Bowel Diseases*, *28*(6), 862–869. https://doi.org/10.1093/ibd/izab192

[19] US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2016). *Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry*. pg.4.

[20] Ibid, pg. 3.

[21] AbbVie. (2023). *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Upadacitinib (ABT-494) for the Induction of Symptomatic and Endoscopic Remission in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Immunomodulators or Anti-TNF Therapy* (Clinical Trial Registration NCT02365649). https://clinicaltrials.gov/study/NCT02365649

- **Primary endpoint:** Percentage of Participants Who Achieve Clinical Remission at Week 16.
- Clinical remission: Average daily stool frequency ≤ 1.5 and not worse than Baseline AND average daily abdominal pain ≤ 1.0 and not worse than Baseline.
- Abdominal Pain was rated on a 4-point scale from 0 (none) to 3 (severe).

2. Migraines
   - Migraines and CP alike are episodic, pain-driven, and have an unpredictable disease pattern with certain triggers.
   - Migraines and other types of headaches have a **well established regulatory precedent for utilizing patient-reported episodic flares as endpoints** in clinical trials.
   - Diagnostic criteria for frequent episodic-type headaches[22]
     1. At least 10 episodes of headache occurring on 1-14 days/month on average for >3 months (≥12 and <180 days/year)
     2. Lasting from 30 minutes to 7 days
     3. At least two of the following four characteristics: bilateral location, pressing or tightening (non-pulsating) quality, mild or moderate intensity, and /or not aggravated by routine physical activity such as walking or climbing stairs
     4. Both of the following: no nausea or vomiting, and no more than one of photophobia or phonophobia
     5. Not better accounted for by another ICHD (International Classification of Headache Disorder)-3 diagnosis.
   - Diagnostic criteria is heavily reliant on patient reported outcomes (PROs) similar to how CP flares are experienced and communicated.
     - Establishes regulatory precedent on definition and criteria focused on frequency, duration, and symptoms characteristics reported by patient.
   - **Primary endpoints** in migraine prevention trials consistently use change from baseline in monthly migraine days or attacks / reduction in monthly migraine days.[23]

[22] Gobel, H. (n.d.). *2.2 Frequent episodic tension-type headache*. ICHD-3. Retrieved June 30, 2025, from https://ichd-3.org/2-tension-type-headache/2-2-frequent-episodic-tension-type-headache/
[23] US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2023). *Migraine: Developing Drugs for Preventive Treatment Guidance for Industry*. pg.5.

- For acute migraine trials, two **co-primary endpoints** are: 1) having no headache pain at 2 hours after dosing & 2) absence of most bothersome symptoms at 2 hours after dose (PRO-based endpoints).[24]
    - The FDA guidance for acute treatment recommends the use of the 4 point Likert scale for headache pain (0 = none, 1 = mild, 2 = moderate, 3 = severe).[25]
    - The FDA guidance for preventive treatment clearly states that "In clinical studies for migraine, the primary endpoint is typically patient reported."[26]
- FDA approved drugs have used these endpoints
    - E.g. Eptinezumab-jjmr (VYEPTI™) approved by FDA using "reduction in migraine days" as the primary endpoint.[27]

3. Systemic Lupus Erythematosus (SLE)
    - Its similarities to CP lie in its episodic nature, unpredictable flare patterns, and multi-organ involvement.
    - SLE relies on flare-based outcome measures accepted by the FDA.
    - **Flare definition**: Clinical worsening requiring treatment escalation, often assessed with SLEDAI or BILAG disease activity indices.[28]
        - SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) is the scoring system used to assess disease activity in SLE. It evaluates the presence and severity of 11 clinical and laboratory measures over 10 days including rash, photosensitivity, alopecia, renal disease, amongst others.[29]

[24] US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2018). *Migraine: Developing Drugs for Acute Treatment Guidance for Industry*. pg.4.
[25] Ibid, pg.5.
[26] US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2023). *Migraine: Developing Drugs for Preventive Treatment Guidance for Industry*. pg.5.
[27] American Headache Society. (n.d.). *Breaking News: Eptinezumab-jjmr (VYEPTI™) Approved by FDA*. American Headache Society. Retrieved June 30, 2025, from https://americanheadachesociety.org/research/library/breaking-news-eptinezumab-jjmr-vyepti-approved-by-fda
[28] Adamichou, C., & Bertsias, G. (2017). Flares in systemic lupus erythematosus: Diagnosis, risk factors and preventive strategies. *Mediterranean Journal of Rheumatology*, *28*(1), 4–12. https://doi.org/10.31138/mjr.28.1.4
[29] Tofighi, T., Morand, E. F., & Touma, Z. (2021). Systemic Lupus Erythematosus Outcome Measures for Systemic Lupus Erythematosus Clinical Trials. *Rheumatic Disease Clinics of North America*, *47*(3), 415–426. https://doi.org/10.1016/j.rdc.2021.04.007

    - BILAG (British Isles Lupus Assessment Group) focuses specifically on the clinical manifestations of lupus across different organ systems, scoring them from A (very active) to E (inactive).[30]
- "...majority of SLE patients experience repeat exacerbations (flares) during the disease course…described as a significant risk factor for development of irreversible end-organ damage. Accordingly, **prevention of flares has been recognized as a distinct therapeutic target** in SLE and involves adequate control of disease activity, use of hydroxychloroquine, maintaining immunosuppressive or biologic therapy for several years, and avoiding non-compliance issues."[31]
- The FDA Guidance for Industry Developing Medical Products for Treatment has specified acceptable endpoints for SLE.
    - **Primary endpoints:** "Reduction in disease activity, complete clinical response or remission, reduction in flare / increase in time to flare, reduction in concomitant steroids, treatment of serious acute manifestations".[32]
    - As per the FDA guidance, the "primary endpoint for a trial evaluating flares can be a reduction in flares or an increase in the time to flare for the new medical product compared to the control group. If time to flare is evaluated as the primary endpoint, the trial should be at least 1 year in duration to evaluate whether the flares are suppressed or only delayed in occurrence. A critical secondary endpoint should be comparison of flare rates or proportion of patients flare-free at an appropriate time point."[33]
        - It is important to include a definition of what a flare entails in the protocol and should reflect an episode of increased disease activity that correlates with the need for an increase in or change in treatment on clinical grounds.
        - Flares can be adjudicated by a data monitoring board, blinded to treatment.[34]

[30] Carter, L. M., Gordon, C., Yee, C.-S., Bruce, I., Isenberg, D., Skeoch, S., & Vital, E. M. (2022). Easy-BILAG: A new tool for simplified recording of SLE disease activity using BILAG-2004 index. *Rheumatology (Oxford, England)*, *61*(10), 4006–4015. https://doi.org/10.1093/rheumatology/keab883

[31] Adamichou, C., & Bertsias, G. (2017). Flares in systemic lupus erythematosus: Diagnosis, risk factors and preventive strategies. *Mediterranean Journal of Rheumatology*, *28*(1), 4–12. https://doi.org/10.31138/mjr.28.1.4

[32] Research, C. for D. E. and. (2020, May 5). *Systemic Lupus Erythematosus—Developing Medical Products for Treatment*. FDA. pg.5. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/systemic-lupus-erythematosus-developing-medical-products-treatment

[33] Research, C. for D. E. and. (2020, May 5). *Systemic Lupus Erythematosus—Developing Medical Products for Treatment*. FDA. pg.10. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/systemic-lupus-erythematosus-developing-medical-products-treatment

[34] Ibid, pg.8.

- E.g. Anifrolumab (Saphnelo) is a human antibody manufactured by AstraZeneca that is used to treat SLE and uses flare reduction as an outcome.
    - **Secondary Endpoint**: Annualized flare rate.[35]
    - "Flare defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items as compared with the previous visit".[36]

4. Rheumatoid Arthritis (RA)
    - RA is a chronic, systemic inflammation with episodic symptom spikes where PROs are central to assessment.
    - **Flare definition:** Patient perceived increase in pain, fatigue, or stiffness, classified via validated PRO tools.
        - Patients and rheumatologists refer to severe and debilitating episodes of disease worsening as "flares". Flares can vary in frequency, duration, and intensity.[37]
    - The OMERACT RA Flare Questionnaire was developed as a patient-reported outcome tool to assess active flares.[38]
        - Core domain sets: pain intensity, pain interference, physical function, fatigue, patient global assessment, health related quality of life.
        - Pain interference: "Consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical and recreational activities.[39]
        - Pain intensity: "The intensity of the sensation of pain, encompassing the entire spectrum from a complete absence of pain to the most extreme levels of discomfort."[40]

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[35] Morand, E. F., Furie, R., Tanaka, Y., Bruce, I. N., Askanase, A. D., Richez, C., Bae, S.-C., Brohawn, P. Z., Pineda, L., Berglind, A., & Tummala, R. (2020). Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *New England Journal of Medicine*, *382*(3), 211–221. https://doi.org/10.1056/NEJMoa1912196

[36] Ibid.

[37] Bykerk, V. P., Bingham, C. O., Choy, E. H., Lin, D., Alten, R., Christensen, R., Furst, D. E., Hewlett, S., Leong, A., March, L., Woodworth, T., Boire, G., Haraoui, B., Hitchon, C., Jamal, S., Keystone, E. C., Pope, J., Tin, D., Thorne, J. C., & Bartlett, S. J. (2016). Identifying flares in rheumatoid arthritis: Reliability and construct validation of the OMERACT RA Flare Core Domain Set. *RMD Open*, *2*(1), e000225. https://doi.org/10.1136/rmdopen-2015-000225

[38] Bykerk, V. P., Shadick, N., Frits, M., Bingham, C. O., Jeffery, I., Iannaccone, C., Weinblatt, M., & Solomon, D. H. (2014). Flares in rheumatoid arthritis: Frequency and management. A report from the BRASS registry. *The Journal of Rheumatology*, *41*(2), 227–234. https://doi.org/10.3899/jrheum.121521

[39] Bykerk, V. P., Lie, E., Bartlett, S. J., Alten, R., Boonen, A., Christensen, R., Furst, D. E., Hewlett, S., Leong, A. L., Lyddiatt, A., March, L., May, J. E., Montie, P., Orbai, A.-M., Pohl, C., Voshaar, M. S., Woodworth, T., Bingham, C. O., & Choy, E. H. (2014). Establishing a Core Domain Set to Measure Rheumatoid Arthritis Flares: Report of the OMERACT 11 RA Flare Workshop. *The Journal of Rheumatology*, *41*(4), 799–809. https://doi.org/10.3899/jrheum.131252

[40] Ibid.

    - Patients who classified themselves as flaring then rated the severity using an 11-point Numerical Rating Scale (NRS). This tool is unidimensional, with a focus on intensity of pain.[41]
- The FDA guidance acknowledges OMERACT as a key initiative to the development of validated outcome measures for rheumatoid arthritis, including tools to assess disease activity and patient-reported symptoms, which may be used to support clinical trial endpoints.[42]
    - If a flare design is employed, active-controlled trials should incorporate a placebo arm in order to compare to baseline
- PROs commonly used in RA studies include the RAND-12 Rheumatoid Arthritis Disease Activity Index (RADAI) & Work Productivity and Activity Impairment-Rheumatoid Arthritis (WPAI-RA) Questionnaire (legacy PROs).[43]
    - Legacy PROs refer to traditional patient-reported outcome measures (PROMs) that have been used for many years in clinical research.
- E.g. ARCTIC REWIND TNFi-Inhibitor withdrawal in RA.[44]
    - Patients with RA in sustained remission ≥ 12 months on stable TNF-inhibitor therapy were randomized to taper TNF-inhibitors or continue full dose therapy.
    - **Primary endpoint**: Disease flare incidence during the 12 month study period.
    - **Flare was defined** using Disease Activity Score-28 with C-reactive protein (DAS28-CRP) thresholds. To be categorized as a disease flare, all three following criteria had to be met:
        - DAS > 1.6 (above remission threshold).

[41] Bykerk, V. P., Bingham, C. O., Choy, E. H., Lin, D., Alten, R., Christensen, R., Furst, D. E., Hewlett, S., Leong, A., March, L., Woodworth, T., Boire, G., Haraoui, B., Hitchon, C., Jamal, S., Keystone, E. C., Pope, J., Tin, D., Thorne, J. C., & Bartlett, S. J. (2016). Identifying flares in rheumatoid arthritis: Reliability and construct validation of the OMERACT RA Flare Core Domain Set. *RMD Open*, *2*(1), e000225. https://doi.org/10.1136/rmdopen-2015-000225

[42] US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (1999). *Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)*. pg.2. https://www.fda.gov/media/71145/download

[43] Bykerk, V. P., Bingham, C. O., Choy, E. H., Lin, D., Alten, R., Christensen, R., Furst, D. E., Hewlett, S., Leong, A., March, L., Woodworth, T., Boire, G., Haraoui, B., Hitchon, C., Jamal, S., Keystone, E. C., Pope, J., Tin, D., Thorne, J. C., & Bartlett, S. J. (2016). Identifying flares in rheumatoid arthritis: Reliability and construct validation of the OMERACT RA Flare Core Domain Set. *RMD Open*, *2*(1), e000225. https://doi.org/10.1136/rmdopen-2015-000225

[44] Lillegraven, S., Paulshus Sundlisæter, N., Aga, A.-B., Sexton, J., Olsen, I. C., Lexberg, Å. S., Madland, T. M., Fremstad, H., Høili, C. A., Bakland, G., Spada, C., Haukeland, H., Hansen, I. M., Moholt, E., Uhlig, T., Solomon, D. H., Van Der Heijde, D., Kvien, T. K., & Haavardsholm, E. A. (2023). Effect of tapered versus stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: A randomised, open label, non-inferiority trial. *Annals of the Rheumatic Diseases*, *82*(11), 1394–1403. https://doi.org/10.1136/ard-2023-224476

- Increase in DAS ≥ 0.6 units from prior visit.
- ≥ 2 swollen joints on a 44-joint exam.

  - Alternatively, a patient could also be considered to have a flare if "the patient and investigator agreed that a clinically significant flare had occurred".[45] The patient completed the OMERACT Rheumatoid Arthritis Flare Questionnaire (RA-FQ), rating their perspective of their RA symptoms on a 1-10 scale, 0 being no pain, and 10 being extreme pain. The questionnaire explicitly includes the question "Are you having a flare of your RA at this time?"[46]
  - Flare events were adjudicated and used to compare treatment durability.

5. Fibrodysplasia Ossificans Progressiva (FOP)
   - Rare progressive disease characterized by progressive heterotopic ossification (HO) and painful soft tissue inflammatory flare ups. Pain and disability are core outcomes.
   - **Flare definition**: Patient-reported flare-ups defined with onset of at least two of the following - new or worsened pain, swelling, stiffness, reduced motion, or presumed heterotopic ossification.[47]
     - PRO-based flare diaries assessing presence and duration
     - For instance, a daily electronic diary, eDiary, was developed specifically for the study by Regeneron.[48]

[45] Lillegraven, S., Paulshus Sundlisæter, N., Aga, A.-B., Sexton, J., Olsen, I. C., Lexberg, Å. S., Madland, T. M., Fremstad, H., Høili, C. A., Bakland, G., Spada, C., Haukeland, H., Hansen, I. M., Moholt, E., Uhlig, T., Solomon, D. H., Van Der Heijde, D., Kvien, T. K., & Haavardsholm, E. A. (2023). Effect of tapered versus stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: A randomised, open label, non-inferiority trial. *Annals of the Rheumatic Diseases*, *82*(11), 1394–1403. https://doi.org/10.1136/ard-2023-224476

[46] Holten, K., Paulshus Sundlisæter, N., Sexton, J., Kjørholt, K. E., Nordberg, L. B., Moholt, E., Uhlig, T., van der Heijde, D., Solomon, D. H., Haavardsholm, E. A., Lillegraven, S., & Aga, A.-B. (2024). Agreement between patient-reported flares and clinically significant flare status in patients with rheumatoid arthritis in sustained remission: Data from the ARCTIC REWIND trials. *RMD Open*, *10*(3), e004444. https://doi.org/10.1136/rmdopen-2024-004444

[47] Keen, R., Dahir, K. M., McGinniss, J., Sanchez, R. J., Mellis, S., Economides, A. N., Di Rocco, M., Orcel, P., Roux, C., Tabarkiewicz, J., Bachiller-Corral, J., Cheung, A. M., Al Mukaddam, M., Mohammadi, K., Gu, J., Srinivasan, D., Trotter, D. G., Eekhoff, E. M. W., Kaplan, F. S., & Pignolo, R. J. (2024). Characterization of flare-ups and impact of garetosmab in adults with fibrodysplasia ossificans progressiva: A post hoc analysis of the randomized, double-blind, placebo-controlled LUMINA-1 trial. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, *39*(10), 1486–1492. https://doi.org/10.1093/jbmr/zjae140

[48] Di Rocco, M., Forleo-Neto, E., Pignolo, R. J., Keen, R., Orcel, P., Funck-Brentano, T., Roux, C., Kolta, S., Madeo, A., Bubbear, J. S., Tabarkiewicz, J., Szczepanek, M., Bachiller-Corral, J., Cheung, A. M., Dahir, K. M., Botman, E., Raijmakers, P. G., Al Mukaddam, M., Tile, L., … Kaplan, F. S. (2023). Garetosmab in fibrodysplasia ossificans progressiva: A randomized, double-blind, placebo-controlled phase 2 trial. *Nature Medicine*, *29*(10), 2615–2624. https://doi.org/10.1038/s41591-023-02561-8

- E.g. LUMINA-1 trial: Garetosmab, anti-activin A monoclonal antibody, manufactured by Regeneron Pharmaceuticals.
    - **Secondary and exploratory endpoint**: "Percentage of patients with flare-ups as assessed by patient diary and post-hoc analyses included investigator reported flare-ups."[49]
    - "Patient-reported flare-ups were defined by any 2 of the following: new onset of pain, swelling, joint stiffness, decrease in movement, or perceived presence of HO."[50]

6. Polymyalgia Rheumatica (PMR)
    - Inflammatory condition that causes widespread muscle pain and stiffness, typically in the shoulders, neck, hips, and upper arms.[51]
    - **Secondary endpoint** for KEVZARA® (sarilumab) by Sanofi and Regeneron Pharmaceuticals, Inc: Absence of disease flare (sustained remission).[52]
        - Sustained remission defined as "the resolution of signs and symptoms of polymyalgia rheumatica by week 12 and sustained normalization of the C-reactive protein level, absence of disease flare, and adherence to the prednisone taper from weeks 12 through 52."[53]
        - For this trial, a disease flare was defined as the recurrence of PMR signs/symptoms plus an increase in corticosteroid dose, or elevated erythrocyte sedimentation rate (ESR) alongside increased steroid dose.

Across these 6 conditions, regulators accept flare definitions that combine patient reporting with objective adjudication, especially when episodes reflect functional loss and treatment escalation.

**II. Pancreatitis: Defining and Measuring Flares**

How Pancreatitis Patients Experience Flares

Patient narratives further illustrate the debilitating nature of flares. In the National Pancreas Foundation's "Voice of the Patient" report, several patients describe the profound impact of these episodes.

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[49] Ibid.

[50] Keen, R., Dahir, K. M., McGinniss, J., Sanchez, R. J., Mellis, S., Economides, A. N., Di Rocco, M., Orcel, P., Roux, C., Tabarkiewicz, J., Bachiller-Corral, J., Cheung, A. M., Al Mukaddam, M., Mohammadi, K., Gu, J., Srinivasan, D., Trotter, D. G., Eekhoff, E. M. W., Kaplan, F. S., & Pignolo, R. J. (2024). Characterization of flare-ups and impact of garetosmab in adults with fibrodysplasia ossificans progressiva: A post hoc analysis of the randomized, double-blind, placebo-controlled LUMINA-1 trial. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, *39*(10), 1486–1492. https://doi.org/10.1093/jbmr/zjae140

[51] *Polymyalgia rheumatica—Symptoms & causes—Mayo Clinic*. (n.d.). Retrieved July 6, 2025, from https://www.mayoclinic.org/diseases-conditions/polymyalgia-rheumatica/symptoms-causes/syc-20376539

[52] *KEVZARA® (sarilumab) | KEVZARA (sarilumab) injection 200 mg*. (n.d.). KEVZARA® (Sarilumab) Patient Website. Retrieved June 30, 2025, from https://www.kevzara.com/ra/

[53] Ibid.

- "The flare-ups are the worst parts. At those points, I am not at 50%; I'm at 5%, much worse than say having the flu. I'm drained of all energy, nauseous, weak, bedridden, barely able to function, in horrible pain, and unable to eat any solid food for up to five days at a time."[54]
- Lindsey's story: "Twice, I had a cheeseburger at parties/events and ended up in the hospital with a flare."[55]
- Logan's story: "When he is in a sub-acute flare he is couch bound and not able/willing to engage in activity. When it becomes an acute flare he stops being able to walk upright. He will tell us every step is "punches to my pancreas." He stops eating, he stops drinking and the pain creates a desperation for him. His hunched walk is a tell-tale sign we are on our way to an admission."[56]

Defining Flares

The most widely recognized clinical definition for acute pancreatitis is the Revised Atlanta Classification (2012), which requires at least two of the following: (1) abdominal pain consistent with pancreatitis, (2) serum lipase or amylase ≥3 times the upper limit of normal, and (3) characteristic findings of pancreatitis on imaging.[57] This standard has also been applied in flare-based endpoints for drug trials involving acute or recurrent pancreatitis.

However, chronic pancreatitis (CP) flares may not meet Atlanta criteria because enzyme levels may not increase substantially and imaging may not change.[58] Alternative definitions are necessary to reflect real-world CP symptom exacerbations. Other factors to consider include:

- Patient-reported pain spike using a validated instrument
- Medication use: New or increased use of opioids or other pain medication
- Functional impact: Emergency department visits, hospitalizations, missed work/school, significant activity limitation

Clarifying Terminology: Flares vs. Acute Pancreatitis

[54] Staff, N. P. F. (n.d.). *PFDD Voice of The Patient*. National Pancreas Foundation. pg.7. Retrieved June 30, 2025, from https://pancreasfoundation.org/patient-resources/pfdd-voice-of-the-patient/
[55] Tun, S. (2021, December 13). *Lindsey's Story*. National Pancreas Foundation. https://pancreasfoundation.org/stories/lindseys-story/
[56] Tun, S. (2020, May 5). *Logan's Story*. National Pancreas Foundation. https://pancreasfoundation.org/stories/logans-story/
[57] Sarr, M. G. (2013). 2012 revision of the Atlanta classification of acute pancreatitis. *Polskie Archiwum Medycyny Wewnetrznej*, *123*(3), 118–124. https://doi.org/10.20452/pamw.1627
[58] Drewes, A. M., van Veldhuisen, C. L., Bellin, M. D., Besselink, M. G., Bouwense, S. AW., Olesen, S. S., van Santvoort, H., Vase, L., & Windsor, J. A. (2021). Assessment of pain associated with chronic pancreatitis: An international consensus guideline. *Pancreatology*, *21*(7), 1256–1284. https://doi.org/10.1016/j.pan.2021.07.004

Two terms are used to refer to the severe, episodic exacerbations of symptoms (primarily pain) that pancreatitis patients suffer: chronic pancreatitis flares and acute pancreatitis (AP) attacks. An acute pancreatitis attack or episode is defined by the Revised Atlanta 2012 Classification and requires two or more of the following: significant elevation of pancreatic enzyme levels, upper abdominal pain, or characteristic findings on imaging.[59] When patients have had chronic pancreatitis for an extended period, their enzyme levels may not elevate when they have a flare or acute attack.[60] These terms are often used interchangeably in both scientific and patient communities. For instance, in Ionis's Olezarsen trial, acute pancreatitis episodes were classified and treated as flare events. Similarly, patient narratives frequently refer to "flares" that meet AP diagnostic criteria. Though the use of these two terms presents a complication, with thoughtful definitions and consistent adjudication, flares can still serve as a discrete, clinically meaningful outcome.

From a regulatory perspective, a clinical outcome assessment (COA) is considered **fit-for-purpose** when it is scientifically sound, validated, and appropriately tailored to measure a specific concept within a particular context of use, such as a chronic disease population or clinical trial endpoint. Fit-for-purpose tools may be adapted from existing validated measures or newly developed when no adequate alternatives exist; the FDA encourages this in the case of rare diseases. For example, in the LUMINA-1 trial for Fibrodysplasia Ossificans Progressiva (FOP), a custom electronic diary was used to capture patient-reported flare activity in the absence of validated instruments. The diary was developed by the sponsor and used prospectively.[61] As noted in the FDA Guidance for Industry for Rare Diseases, the “FDA advises sponsors to consider using or modifying existing measures for the disease under study because evaluating novel measures is time consuming”.[62]

Possible Trial Endpoints

- Time to first adjudicated flare
- Reduction in flare frequency over a defined treatment period
- Average flare duration

[59] Sarr, M. G. (2013). 2012 revision of the Atlanta classification of acute pancreatitis. *Polskie Archiwum Medycyny Wewnetrznej*, *123*(3), 118–124. https://doi.org/10.20452/pamw.1627

[60] Drewes, A. M., van Veldhuisen, C. L., Bellin, M. D., Besselink, M. G., Bouwense, S. AW., Olesen, S. S., van Santvoort, H., Vase, L., & Windsor, J. A. (2021). Assessment of pain associated with chronic pancreatitis: An international consensus guideline. *Pancreatology*, *21*(7), 1256–1284. https://doi.org/10.1016/j.pan.2021.07.004

[61] Di Rocco, M., Forleo-Neto, E., Pignolo, R. J., Keen, R., Orcel, P., Funck-Brentano, T., Roux, C., Kolta, S., Madeo, A., Bubbear, J. S., Tabarkiewicz, J., Szczepanek, M., Bachiller-Corral, J., Cheung, A. M., Dahir, K. M., Botman, E., Raijmakers, P. G., Al Mukaddam, M., Tile, L., … Kaplan, F. S. (2023). Garetosmab in fibrodysplasia ossificans progressiva: A randomized, double-blind, placebo-controlled phase 2 trial. *Nature Medicine*, *29*(10), 2615–2624. https://doi.org/10.1038/s41591-023-02561-8

[62] US Department of Health and Human Services, & Food and Drug Administration. (2023). *Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry*. pg.15.

- Proportion of patients flare-free during treatment

**IV. Conclusion**

Establishing flares as a clinical trial endpoint in chronic pancreatitis is feasible, accepted by regulators, and supported by precedent in related diseases. Flares have already been used in drug trials involving pancreatitis and serve as meaningful, patient-centered outcomes in other chronic conditions such as migraine.

The FDA has demonstrated flexibility in accepting flare endpoints when clearly defined, adjudicated, and measured using validated or fit-for-purpose PRO tools. Incorporating flares into CP trials will require thoughtful design but offers an opportunity to capture real-world disease burden, especially in the absence of definitive biomarkers or structural progression.

In the near term, sponsors should prioritize:

- Establishing or adopting a clear definition of a flare
- Selecting or adapting assessment tools that minimize patient burden while maximizing clinical relevance
- Designing efficient adjudication processes to ensure consistency

Key stakeholders, including regulatory agencies, clinicians, researchers, and patient advocates, must collaborate to refine these definitions and tools.

**Bibliography**

AbbVie. (2023). *A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Upadacitinib (ABT-494) for the Induction of Symptomatic and Endoscopic Remission in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Immunomodulators or Anti-TNF Therapy* (Clinical Trial Registration NCT02365649). https://clinicaltrials.gov/study/NCT02365649

Adamichou, C., & Bertsias, G. (2017). Flares in systemic lupus erythematosus: Diagnosis, risk factors and preventive strategies. *Mediterranean Journal of Rheumatology*, *28*(1), 4–12. https://doi.org/10.31138/mjr.28.1.4

Alten, R. (2011). Tocilizumab: A Novel Humanized Anti-Interleukin 6 Receptor Antibody for the Treatment of Patients with Rheumatoid Arthritis. *Therapeutic Advances in Musculoskeletal Disease*, *3*(3), 133–149. https://doi.org/10.1177/1759720x11407540

American Headache Society. (n.d.). *Breaking News: Eptinezumab-jjmr (VYEPTI™) Approved by FDA*. American Headache Society. Retrieved June 30, 2025, from https://americanheadachesociety.org/research/library/breaking-news-eptinezumab-jjmr-vyepti-approved-by-fda

Amgen. (2025). *A Phase 3, Randomized, Double-blind, Multicenter, Placebo Controlled Study of Inebilizumab Efficacy and Safety in IgG4-Related Disease* (Clinical Trial Registration NCT04540497). https://clinicaltrials.gov/study/NCT04540497

Atkinson, T. M., Mendoza, T. R., Sit, L., Passik, S., Scher, H. I., Cleeland, C., & Basch, E. (2010). The Brief Pain Inventory and its “Pain at its Worst in the last 24 Hours” Item: Clinical Trial Endpoint Considerations. *Pain Medicine (Malden, Mass.)*, *11*(3), 337–346. https://doi.org/10.1111/j.1526-4637.2009.00774.x

Bristol-Myers Squibb. (2016). *A Phase III, Multi-Center, Multi-National, Randomized Withdrawal Study to Evaluate the Safety and Efficacy of BMS-188667 in Children and Adolescents With Active Polyarticular Juvenile Rheumatoid Arthritis (JRA)* (Clinical Trial Registration NCT00095173). https://clinicaltrials.gov/study/NCT00095173

Bykerk, V. P., Bingham, C. O., Choy, E. H., Lin, D., Alten, R., Christensen, R., Furst, D. E., Hewlett, S., Leong, A., March, L., Woodworth, T., Boire, G., Haraoui, B., Hitchon, C., Jamal, S., Keystone, E. C., Pope, J., Tin, D., Thorne, J. C., & Bartlett, S. J. (2016). Identifying flares in rheumatoid arthritis: Reliability and construct validation of the OMERACT RA Flare Core Domain Set. *RMD Open*, *2*(1), e000225. https://doi.org/10.1136/rmdopen-2015-000225

Bykerk, V. P., Lie, E., Bartlett, S. J., Alten, R., Boonen, A., Christensen, R., Furst, D. E., Hewlett, S., Leong, A. L., Lyddiatt, A., March, L., May, J. E., Montie, P., Orbai, A.-M., Pohl, C., Voshaar, M. S., Woodworth, T., Bingham, C. O., & Choy, E. H. (2014). Establishing a Core Domain Set to Measure Rheumatoid Arthritis Flares: Report of the OMERACT 11 RA Flare Workshop. *The Journal of Rheumatology*, *41*(4), 799–809. https://doi.org/10.3899/jrheum.131252

Bykerk, V. P., Shadick, N., Frits, M., Bingham, C. O., Jeffery, I., Iannaccone, C., Weinblatt, M., & Solomon, D. H. (2014). Flares in rheumatoid arthritis: Frequency and management. A report from the BRASS registry. *The Journal of Rheumatology*, *41*(2), 227–234. https://doi.org/10.3899/jrheum.121521

Carruthers, M. N., Topazian, M. D., Khosroshahi, A., Witzig, T. E., Wallace, Z. S., Hart, P. A., Deshpande, V., Smyrk, T. C., Chari, S., & Stone, J. H. (2015). Rituximab for IgG4-related disease: A prospective, open-label trial. *Annals of the Rheumatic Diseases*, *74*(6), 1171–1177. https://doi.org/10.1136/annrheumdis-2014-206605

Carter, L. M., Gordon, C., Yee, C.-S., Bruce, I., Isenberg, D., Skeoch, S., & Vital, E. M. (2022). Easy-BILAG: A new tool for simplified recording of SLE disease activity using BILAG-2004 index. *Rheumatology (Oxford, England)*, *61*(10), 4006–4015. https://doi.org/10.1093/rheumatology/keab883

Di Rocco, M., Forleo-Neto, E., Pignolo, R. J., Keen, R., Orcel, P., Funck-Brentano, T., Roux, C., Kolta, S., Madeo, A., Bubbear, J. S., Tabarkiewicz, J., Szczepanek, M., Bachiller-Corral, J., Cheung, A. M., Dahir, K. M., Botman, E., Raijmakers, P. G., Al Mukaddam, M., Tile, L., … Kaplan, F. S. (2023). Garetosmab in fibrodysplasia ossificans progressiva: A randomized, double-blind, placebo-controlled phase 2 trial. *Nature Medicine*, *29*(10), 2615–2624. https://doi.org/10.1038/s41591-023-02561-8

Drewes, A. M., van Veldhuisen, C. L., Bellin, M. D., Besselink, M. G., Bouwense, S. AW., Olesen, S. S., van Santvoort, H., Vase, L., & Windsor, J. A. (2021). Assessment of pain associated with chronic pancreatitis: An international consensus guideline. *Pancreatology*, *21*(7), 1256–1284. https://doi.org/10.1016/j.pan.2021.07.004

Gagyi, E.-B., Teutsch, B., Veres, D. S., Pálinkás, D., Vörhendi, N., Ocskay, K., Márta, K., Hegyi, P. J., Hegyi, P., & Erőss, B. (2024). Incidence of recurrent and chronic pancreatitis after acute pancreatitis: A systematic review and meta-analysis. *Therapeutic Advances in Gastroenterology*, *17*, 17562848241255303. https://doi.org/10.1177/17562848241255303

Genovese, M. C., McKay, J. D., Nasonov, E. L., Mysler, E. F., da Silva, N. A., Alecock, E., Woodworth, T., & Gomez-Reino, J. J. (2008). Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with

traditional disease-modifying antirheumatic drug therapy study. *Arthritis & Rheumatism*, *58*(10), 2968–2980. https://doi.org/10.1002/art.23940

Gobel, H. (n.d.). *2.2 Frequent episodic tension-type headache*. ICHD-3. Retrieved June 30, 2025, from https://ichd-3.org/2-tension-type-headache/2-2-frequent-episodic-tension-type-headache/

Holten, K., Paulshus Sundlisæter, N., Sexton, J., Kjørholt, K. E., Nordberg, L. B., Moholt, E., Uhlig, T., van der Heijde, D., Solomon, D. H., Haavardsholm, E. A., Lillegraven, S., & Aga, A.-B. (2024). Agreement between patient-reported flares and clinically significant flare status in patients with rheumatoid arthritis in sustained remission: Data from the ARCTIC REWIND trials. *RMD Open*, *10*(3), e004444. https://doi.org/10.1136/rmdopen-2024-004444

*Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases—ScienceDirect*. (n.d.). Retrieved July 17, 2025, from https://www-sciencedirect-com.revproxy.brown.edu/science/article/pii/S1424390320301265

Ionis Pharmaceuticals, Inc. (2025). *A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEA-APOCIII-LRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)* (Clinical Trial Registration NCT04568434). https://clinicaltrials.gov/study/NCT04568434

Keen, R., Dahir, K. M., McGinniss, J., Sanchez, R. J., Mellis, S., Economides, A. N., Di Rocco, M., Orcel, P., Roux, C., Tabarkiewicz, J., Bachiller-Corral, J., Cheung, A. M., Al Mukaddam, M., Mohammadi, K., Gu, J., Srinivasan, D., Trotter, D. G., Eekhoff, E. M. W., Kaplan, F. S., & Pignolo, R. J. (2024). Characterization of flare-ups and impact of garetosmab in adults with fibrodysplasia ossificans progressiva: A post hoc analysis of

the randomized, double-blind, placebo-controlled LUMINA-1 trial. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, *39*(10), 1486–1492. https://doi.org/10.1093/jbmr/zjae140

*KEVZARA® (sarilumab) | KEVZARA (sarilumab) injection 200 mg*. (n.d.). KEVZARA® (Sarilumab) Patient Website. Retrieved June 30, 2025, from https://www.kevzara.com/ra/

Lillegraven, S., Paulshus Sundlisæter, N., Aga, A.-B., Sexton, J., Olsen, I. C., Lexberg, Å. S., Madland, T. M., Fremstad, H., Høili, C. A., Bakland, G., Spada, C., Haukeland, H., Hansen, I. M., Moholt, E., Uhlig, T., Solomon, D. H., Van Der Heijde, D., Kvien, T. K., & Haavardsholm, E. A. (2023). Effect of tapered versus stable treatment with tumour necrosis factor inhibitors on disease flares in patients with rheumatoid arthritis in remission: A randomised, open label, non-inferiority trial. *Annals of the Rheumatic Diseases*, *82*(11), 1394–1403. https://doi.org/10.1136/ard-2023-224476

Mohy-ud-din, N., & Morrissey, S. (2025). Pancreatitis. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK538337/

Morand, E. F., Furie, R., Tanaka, Y., Bruce, I. N., Askanase, A. D., Richez, C., Bae, S.-C., Brohawn, P. Z., Pineda, L., Berglind, A., & Tummala, R. (2020). Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *New England Journal of Medicine*, *382*(3), 211–221. https://doi.org/10.1056/NEJMoa1912196

*Pancreatitis: Symptoms, Causes & Treatment*. (n.d.). Cleveland Clinic. Retrieved June 30, 2025, from https://my.clevelandclinic.org/health/diseases/8103-pancreatitis

*Polymyalgia rheumatica—Symptoms & causes—Mayo Clinic*. (n.d.). Retrieved July 6, 2025, from https://www.mayoclinic.org/diseases-conditions/polymyalgia-rheumatica/symptoms-causes/syc-20376539

Regmi, M., & Rehman, A. (2025). Familial Hyperchylomicronemia Syndrome. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK551655/

Research, C. for D. E. and. (2020, May 5). *Systemic Lupus Erythematosus—Developing Medical Products for Treatment*. FDA. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/systemic-lupus-erythematosus-developing-medical-products-treatment

Sarr, M. G. (2013). 2012 revision of the Atlanta classification of acute pancreatitis. *Polskie Archiwum Medycyny Wewnetrznej*, *123*(3), 118–124. https://doi.org/10.20452/pamw.1627

Staff, N. P. F. (n.d.). *PFDD Voice of The Patient*. National Pancreas Foundation. Retrieved June 30, 2025, from https://pancreasfoundation.org/patient-resources/pfdd-voice-of-the-patient/

Stone, J. H. (2017). *Rituximab (RTX) for IgG4-related Disease (IgG4-RD): A Prospective,Open-label Trial* (Clinical Trial Registration NCT01584388). https://clinicaltrials.gov/study/NCT01584388

Stone, J. H., Khosroshahi, A., Zhang, W., Torre, E. D., Okazaki, K., Tanaka, Y., Löhr, J. M., Schleinitz, N., Dong, L., Umehara, H., Lanzillotta, M., Wallace, Z. S., Ebbo, M., Webster, G. J., Valle, F. M., Nayar, M. K., Perugino, C. A., Rebours, V., Dong, X., … Culver, E. L. (2025). Inebilizumab for Treatment of IgG4-Related Disease. *New England Journal of Medicine*, *392*(12), 1168–1177. https://doi.org/10.1056/NEJMoa2409712

Stroes, E. S. G., Alexander, V. J., Karwatowska-Prokopczuk, E., Hegele, R. A., Arca, M., Ballantyne, C. M., Soran, H., Prohaska, T. A., Xia, S., Ginsberg, H. N., Witztum, J. L., & Tsimikas, S. (2024). Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia

Syndrome. *New England Journal of Medicine*, *390*(19), 1781–1792. https://doi.org/10.1056/NEJMoa2400201

Tofighi, T., Morand, E. F., & Touma, Z. (2021). Systemic Lupus Erythematosus Outcome Measures for Systemic Lupus Erythematosus Clinical Trials. *Rheumatic Disease Clinics of North America*, *47*(3), 415–426. https://doi.org/10.1016/j.rdc.2021.04.007

Tun, S. (2020, May 5). *Logan's Story*. National Pancreas Foundation. https://pancreasfoundation.org/stories/logans-story/

Tun, S. (2021, December 13). *Lindsey's Story*. National Pancreas Foundation. https://pancreasfoundation.org/stories/lindseys-story/

US Department of Health and Human Services, & Food and Drug Administration. (2023). *Rare Diseases: Considerations for the Development of Drugs and Biological Products Guidance for Industry*. pg.15.

US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (1999). *Guidance for Industry Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis (RA)*. https://www.fda.gov/media/71145/download

US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2016). *Ulcerative Colitis: Clinical Trial Endpoints Guidance for Industry*. pg.4.

US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2018). *Migraine: Developing Drugs for Acute Treatment Guidance for Industry*. pg.4.

US Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER). (2023). *Migraine: Developing Drugs for Preventive Treatment Guidance for Industry*. pg.5.

van Vollenhoven, R. F., Kinnman, N., Vincent, E., Wax, S., & Bathon, J. (2011). Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase II, randomized, placebo-controlled trial. *Arthritis and Rheumatism*, *63*(7), 1782–1792. https://doi.org/10.1002/art.30372

Wassef, W., DeWitt, J., McGreevy, K., Wilcox, M., Whitcomb, D., Yadav, D., Amann, S., Mishra, G., Alkaade, S., Romagnuolo, J., Stevens, T., Vargo, J., Gardner, T., Singh, V., Park, W., Hartigan, C., Barton, B., & Bova, C. (2016). Pancreatitis Quality of Life Instrument: A Psychometric Evaluation. *The American Journal of Gastroenterology*, *111*(8), 1177–1186. https://doi.org/10.1038/ajg.2016.225

Watts, G. F., Rosenson, R. S., Hegele, R. A., Goldberg, I. J., Gallo, A., Mertens, A., Baass, A., Zhou, R., Muhsin, M., Hellawell, J., Leeper, N. J., Gaudet, D., & PALISADE Study Group. (2025). Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. *The New England Journal of Medicine*, *392*(2), 127–137. https://doi.org/10.1056/NEJMoa2409368

Witges, K., Sexton, K., Graff, L. A., Targownik, L. E., Lix, L. M., Haviva, C., Stone, J., Shafer, L. A., Vagianos, K., & Bernstein, C. N. (2021). What Is a Flare? The Manitoba Living With IBD Study. *Inflammatory Bowel Diseases*, *28*(6), 862–869. https://doi.org/10.1093/ibd/izab192

Zhang, L., & Smyrk, T. C. (2010). Autoimmune pancreatitis and IgG4-related systemic diseases. *International Journal of Clinical and Experimental Pathology*, *3*(5), 491–504.