UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

IN RE: TEPEZZA MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION,	No. 23 C 3568 MDL No. 3079
This Document Relates to All Cases	Judge Thomas M. Durkin

The PLC's Memorandum in Support of Proposed Bellwether Protocol

The PLC respectfully requests that the Court enter the Protocol for Selection of Initial Bellwether Discovery Cases and Initial Bellwether Trial Cases attached as Exhibit 1. Entering this protocol now sets the stage for an efficient MDL that will serve the legitimate litigation interests of the Court and parties. Plaintiffs' protocol is well tailored to ensure that the litigation proceeds on an efficient path. It does so by permitting specific and general discovery to proceed alongside Defendant's proposed Rule 12 briefing on preemption. This approach avoids undue delay and protects all parties' interest in the efficient resolution of Plaintiffs' claims.

BACKGROUND

The proposed bellwether protocol furthers the efficient progression of this litigation. It sets a filing deadline for cases to be eligible for bellwether consideration. Plaintiffs who file a complaint on or before this deadline then have 30 days to provide Defendant with a substantially completed Plaintiff Profile Form ("PPF"),[1] all medical records in Plaintiff's or Plaintiff's counsel's possession, and medical-record

[1] Defendant has declined to engage in negotiations about a proposed bellwether protocol, including the content of the customary Plaintiff Fact Sheet or Plaintiff Profile Form. If the Court grants this motion, it should direct the parties to negotiate and develop a PPF that will provide information useful to the parties at this stage.

authorizations to permit Defendant to order any additional records. Thereafter, Plaintiffs have 30 days to select three bellwether discovery cases and Defendant has 60 days to select three bellwether discovery cases. Any Rule 12(b)(6) motion practice as to the six selections is due within 30 days of the defense selections, including consolidated briefing on any common issues (*e.g.*, preemption).

Once the six bellwether discovery cases are selected, basic general discovery is to be produced by Defendant and fact discovery commences, which will include the service of a Plaintiff Fact Sheet ("PFS"), Defendant Fact Sheet ("DFS"), and the completion of the depositions of the six Plaintiffs, the medical provider(s) that prescribed Tepezza to Plaintiff, one medical provider that treated Plaintiff's Tepezza-related injury, and one sales representative from Defendant who interacted with each Plaintiff's treating and/or prescribing physicians concerning Tepezza. The proposed protocol allocates a period of 150 days to complete this fact discovery on the six bellwether cases. As soon as the six bellwether discovery cases are selected, Plaintiffs' protocol also permits Defendant to file any Rule 12(b)(6) motions as to any of those six cases.

Phase two of the proposed bellwether protocol contemplates trimming the six bellwether discovery cases to three bellwether trial cases. Of those three cases, one is selected by the PLC, one by Defendant, and one by the Court following input from the parties on representativeness. Ultimately, the Court will also schedule the bellwether trials based on input from the parties.

ARGUMENT

I. The bellwether process should be established now to facilitate efficiency throughout the case.

Now is the ideal time for the Court to enter a bellwether plan. This MDL has been formed and leadership has been appointed to act on behalf of Plaintiffs collectively. A substantial number of cases are already filed (>50 as of this submission) and centralized in this Court. Given the early posture of the litigation, the Court should adopt a bellwether discovery and trial plan to ensure the efficient work-up and resolution of these cases.

Ample guidance supports establishing a bellwether protocol early in litigation. Commenting on the adoption of bellwether protocols, the Manual for Complex Litigation (Fourth) notes:

> Judges often require the parties to submit detailed trial plans early in the case and to modify the plans as the case develops. Such plans assist the court and the parties in determining what issues, claims, and defenses may apply across groups and how to present the proof to a jury. If a mass tort litigation is to proceed by first adjudicating individual test cases, identification of those plaintiffs and discovery into their exposure and injury *should occur at the earliest opportunity*.

Id. at § 22.93 at 463–64 (emphasis supplied). *See also id.* at § 22.316 at 360 ("The judge might also consider setting several individual cases on a schedule for pretrial motions, discovery, and trial as test cases, while holding other cases or claims in abeyance." "Identifying and implementing such approaches promptly will avoid unnecessary delay."). The Guidelines and Best Practices for Large and Mass-Tort MDLs, Bolch Judicial Institute, Duke Law School (Second) provides similar guidance:

> BEST PRACTICE 1C: At an early juncture, the parties and the transferee judge should collaboratively develop a discovery plan.

> One of the most important (and daunting) jobs facing the MDL judge is the "efficient conduct of discovery." (citation omitted). Thus, it is important for a transferee judge to engage counsel leadership at an early stage to develop a workable discovery plan.

Id. at 5. *See also id.* at 6 ("the transferee judges found a clear consensus that a transferee judge needs to 'do everything at once – the endgame, the start game, putting together a great PSC, and a discovery plan.'" The Guidelines further note "[t]he judges recognized that this puts a heavy burden on the transferee judge in the early days of the MDL … but they felt that creating a solid infrastructure as part of a complete litigation plan is essential to success.").

These sources support the proposition that an early bellwether plan is vital to furthering the goals of multidistrict litigation. A bellwether protocol, like the one Plaintiffs propose, allows the court and parties to efficiently manage the litigation *through all aspects of the case.* In particular, Plaintiffs' proposal allows Defendant to test Rule 12 motions; it allows discovery to proceed on both general causation and case-specific issues; it ensures that Rules 702 and 56 motion practice will occur simultaneously; and it allows for the ultimate selection of trial picks.

Courts throughout this District routinely adopt a bellwether protocol *before* Rule 12 motion practice. For example, the PLC's proposal is nearly identical to what Judge Pallmeyer adopted in *In re: Abbott Laboratories, et al., Preterm Infant Nutrition Products Liability Litigation*, MDL No. 3026, N.D. Ill. Case No. 1:22-cv-00071, ECF No. 349.[2] Judge Pallmeyer implemented a bellwether protocol early on

[2] At the prior CMC, Horizon argued the *NEC* MDL was "different" than this case because preemption was previously decided. Hr'g. Tr. at 40-41. Not so. Judge Pallmeyer's Bellwether Protocol afforded Defendants the opportunity to file Rule 12 motions—which they did in several

that ordered the parties to select a limited number of representative cases for discovery work-up as bellwethers and linked Defendants' Rule 12 motion practice to those selections. In short, the MDL will proceed more smoothly and efficiently with Plaintiffs' protocol in place to guide discovery and Rule 12 briefing from the start.

II. The proposed bellwether plan ensures efficient progression of the litigation.

Plaintiffs' protocol strikes the appropriate balance of ensuring the most efficient work-up of general discovery and case-specific bellwether discovery while also prioritizing expedited Rule 12(b)(6) motions by Defendant. In the discovery phase, Plaintiffs' protocol serves the dual purpose of beginning discovery in a select set of cases while also permitting Defendant to test its preemption theories on dismissal motions that can be filed in any or all of those same six cases. The protocol will drive general discovery by tying the onset of case-specific bellwether discovery to the Defendant meeting basic general discovery milestones like producing its BLA file for Tepezza, providing relevant adverse event data, and making a substantial (but not necessarily complete) production of custodial data. The protocol then provides for a reasonable time (150 days) to complete core discovery on the six cases.

Importantly, Plaintiffs' protocol provides Defendant exactly what it has requested. While discussing Plaintiffs' proposed bellwether protocol at the CMC on July 31, Defendant raised a single grievance with Plaintiffs' bellwether protocol. Counsel for Defendant argued against Plaintiffs' protocol because it did not, in

cases. Those motions were resolved *simultaneously* while discovery on general and case-specific causation proceeded.

Defendant's view, sufficiently expedite the briefing of its preemption arguments as to Plaintiffs' failure-to-warn and design defect claims. *See* July 31, 2023 Hr'g Tr. at 36:2–8. This concern, however, is resolved through Plaintiffs' protocol and through the separate agreement to brief preemption as to design-defect claims in an even more expedited fashion (through the *Williams* briefing).

First, Plaintiffs' protocol permits the immediate filing of 12(b)(6) motions by Defendant on any or all of the six discovery cases. Plaintiffs' proposal requires only a slight adjustment to Defendant's preference, which is that the selected bellwethers will also be used to evaluate Defendants' Rule 12 motions. The protocol additionally permits Defendant to select cases from 2020, 2021, and 2022, as it has specifically requested in prior discussions with Plaintiffs' leadership and during the last status hearing. *Id*. at 42:9–13. Thus, Defendant gets precisely what it has requested as to the briefing of its preemption arguments on Plaintiffs' failure-to-warn claims.

Second, the Court has separately provided Defendant an expedited briefing schedule on the issue of design-defect preemption such that it will be completed by August 28. *See id*. at 52:7–23. Timing on preemption briefing on failure-to-warn claims will be resolved with the adoption of this bellwether protocol.

Otherwise, Defendant has already agreed that the Court should proceed with a bellwether protocol:

> THE COURT: Well, I guess I'm asking -- I'll ask the defense, are you – is it a matter of your agreeing to these selection of bellwether cases now or when you have adequate information to make a selection that favors you, just like they're going to select four that favor them if four is the right number for each of you. I'm not sure what the proposal is on that.

> But are you opposed to the idea in general, or just need more information?
>
> MS. HAMMOND: Well, no, Your Honor, we're not opposed to the idea in general.

Id. at 54:17–55:2.

Plaintiffs' protocol satisfies Defendant's desire for prompt Rule 12 briefing with the added benefit of not delaying discovery. Defendant has further conceded that such a protocol can reasonably include discovery occur on the same track as the briefing of its preemption arguments. *See id*. at 55:6–12. This is precisely the formula that Plaintiffs' bellwether protocol follows.

III. Defendant's proposal will result in undue delay.

Although Defendant has never submitted a counter to Plaintiffs' proposed bellwether protocol (which the PLC transmitted to defense counsel on July 20), it is Plaintiffs' understanding that Defendant seeks to begin this litigation by having its 12(b)(6) motions decided before engaging in any meaningful discovery. This position is flawed for multiple reasons.

First, it is contrary to the positions espoused by the Manual for Complex Litigation and the Duke Guidelines. As noted above, both authorities encourage the early adoption of discovery plans and bellwether protocols. Plaintiffs' protocol follows this guidance, whereas delaying all discovery until Rule 12 briefing concludes ignores it in favor of an inefficient and one-sided approach that will only serve to unduly delay resolution of this litigation.

Second, Defendant's proposal improperly assumes that Rule 12 motion practice will resolve every case in this MDL. This notion is flawed. Delaying discovery until

after Rule 12 motion practice makes sense only if there is a substantial likelihood that such motions will resolve all pending claims in the MDL. If some of Plaintiffs claims survive under Rule 12, discovery will be necessary and bifurcating Rule 12 motion practice from general and case-specific discovery will only cause delay.

The undisputed facts here demonstrate that even under a scenario most favorable to Defendant, some cases will remain to be litigated following Rule 12 motion practice. Defendant contends that Plaintiffs' claims are preempted because it never possessed "newly acquired information" sufficient to trigger a requirement to alert the Food and Drug Administration ("FDA") of a "Changes Being Effected" ("CBE") to the Tepezza label alerting medical providers of the risk of permanent hearing impairment or loss. But on July 19, 2023, FDA approved the following label changes *as a Section V* warning:

> Hearing Impairment Including Hearing Loss: TEPEZZA may cause severe hearing impairment including hearing loss, *which in some cases may be permanent*. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

See TEPEZZA Prescribing Information (revisions as of July 2023) (attached as Ex. 2). In short, the FDA approved the very warning Plaintiffs contend Defendant should have included. As detailed in the *Williams* sur-reply, Defendant had the power and obligation to strengthen the warning through the CBE process rather than waiting for FDA approval of the label change. *See* ECF 26 at PageID#: 484–87. Because the FDA did approve the label change, there is no preemption.

Because there is no real argument that all Plaintiffs' claims are preempted, discovery is a certainty—a point Defendant has already largely conceded. *See* Hr'g

Tr. at 55:22–56:24 (agreeing to produce BLA upon entry of protective order) and *id.* at 56:25–57:9 (agreeing to identify custodians by August 31). As such, Plaintiffs' bellwether protocol, which provides Defendant an expedited opportunity to brief its preemption arguments while also beginning basic discovery and selecting and working up bellwether cases, strikes the appropriate balance in fairly and efficiently advancing the litigation.

Finally, Plaintiffs anticipate that Defendant may advocate for a lengthy PPF or Plaintiff Fact Sheet (PFS)[3] to be provided by the eligible Plaintiffs before the initial bellwether discovery selections are made, rather than after those selections are made, as contemplated in Plaintiffs' bellwether proposal. That position is flawed. Once again, the Duke Guidelines espouse a position at the outset of litigation similar to that proposed by Plaintiffs here. The Guidelines provide the following:

> Streamlined plaintiff fact sheets (one to two pages) are appropriate in some MDLs to identify quickly some cases that should not have been added to the cases centralized in the MDL in the first instance. In other MDLs, including large mass torts, more extensive plaintiff fact sheets (five to twenty pages) can serve a broader purpose, providing some useful information to the court and parties to *inform selection of bellwether trials* and settlement negotiations. If only a few core questions are required to be completed, the same fact sheet can serve both purposes. Targeted plaintiff fact sheets can be particularly useful in the largest mass-tort MDLs, many of which involve personal-injury claims allegedly caused by pharmaceuticals or medical devices. In such cases, the plaintiff fact sheet should provide sufficient information to permit the parties and the court to determine: (1) product identity (if not

[3] In some instances, the terms PPF and PFS are used as largely interchangeable terms meant to refer to a discovery document provided by a party to address targeted relevant issues in the litigation. For purposes of this memorandum, Plaintiffs refer to the PPF as the initial discovery document intended to provide basic case information that can be used to make bellwether discovery case selections, while the PFS is intended to refer to a more detailed discovery document intended to be used to assist in preparing the case for trial (in lieu of traditional interrogatories and production requests).

> covered in a preliminary product identification disclosure); (2) exposure, alleged injury, and any adverse consequences; (3) date of injury and of notice or discovery of defendant(s)' alleged wrongful conduct; and (4) authorizations for the release of relevant medical and pharmacy records and other relevant fact sources (such as employers, where wage-related claims are asserted).

Id. at 10–11 (emphasis supplied).

Plaintiffs fully support providing a PPF that includes information sufficient for Defendant to identify an individual Plaintiff's Tepezza usage, information about the Tepezza related injury suffered and any treatment provided for that injury, and provide releases for Defendant to obtain medical records. Moreover, as encouraged by the Duke Guidelines, Plaintiffs are further willing to provide a more detailed PFS to assist in the work-up of the bellwether discovery cases after they are selected. This approach will ensure that Defendant has the information it needs to select and work-up bellwether cases while also ensuring an undue discovery burden is not placed on individual plaintiffs who may never have their cases undergo bellwether discovery. In sum, Plaintiffs' bellwether protocol gives each party the opportunity to target key points in discovery and test issues that will ultimately drive the resolution of this litigation. Plaintiffs' approach further ensures that the litigation will progress efficiently.

CONCLUSION

For those reasons, the PLC respectfully requests that the Court adopt its Proposed Protocol for Selection of Initial Bellwether Discovery Cases and Initial Bellwether Trial Cases as attached to this memorandum.

Dated: August 21, 2023

Respectfully submitted,

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EXHIBIT 1

UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

IN RE: TEPEZZA MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION,	No. 23 C 3568 MDL No. 3079
This Document Relates to All Cases	Judge Thomas M. Durkin

Proposed Protocol for Selection of Initial Bellwether Discovery Cases and Initial Bellwether Trial Cases

I. Scope of Order

In furtherance of the effective and efficient case management of complex litigation, this Case Management Order will govern the guidelines and procedures for selecting a first wave of six cases for which individual case-specific discovery will be conducted (the "Initial Bellwether Discovery Cases"), and then for selecting a smaller subset of three cases thereafter to be designated to be tried as bellwether cases in this MDL Proceeding (the "Initial Bellwether Trial Cases").

II. Determination of cases eligible for Initial Bellwether Discovery Cases

Cases filed on or before **(insert date estimated to be two weeks after entry of order)** shall be eligible to be selected as an Initial Bellwether Discovery Case. All Plaintiffs with a case filed in this MDL are to provide the Defendant a substantially completed Plaintiff Profile Form ("PPF") and medical record authorizations, in the form attached as Exhibits A–C, on or before **(insert date 30 days after filing cutoff date for inclusion in bellwether pool).** In addition, each Plaintiff shall provide at the same time all medical records related to the case that are in the Plaintiff's or Plaintiff's counsel's possession.

III. Selection of Initial Bellwether Discovery Cases

A. From the cases eligible to be selected as Initial Bellwether Discovery Cases, six shall be selected utilizing the following process:

1. Plaintiffs' Selections. On or before **(insert date 30 days after PPF submission deadline date)** Plaintiff's Co-Lead Counsel shall provide to Defendant their selections of three Initial Bellwether Discovery Cases from among the eligible cases.

2. Defendant's Selections. On or before **(insert date 30 days after Plaintiffs' bellwether selection date)** Defendant shall provide to Plaintiffs' Co-Lead Counsel its selections of three Initial Bellwether Discovery Cases from among the eligible cases. Upon the selection of Defendant's Initial Bellwether Discovery Cases, the parties shall jointly submit the complete list of the six Initial Bellwether Discovery cases to the Court via a proposed Order identifying each case so selected by the parties.

B. In selecting their respective Initial Bellwether Discovery Cases, the parties shall select cases that they have a good-faith belief are representative of the body of then-filed cases as a whole, and that should be subject to discovery and then taken to trial.

IV. Fact discovery on Initial Bellwether Discovery Cases

A. Following entry of an Order identifying any cases as an Initial Bellwether Discovery Case:

1. The Plaintiff in such case shall serve a completed Plaintiff Fact Sheet ("PFS") within 30 days of the Order. The form and substance of the PFS to be served will be approved by a separate Order.

2. The Defendant in such case shall serve a completed Defendant Fact Sheet ("DFS") within 30 days of the deadline for service of the PFS. The form and substance of the DFS to be served will be approved by a separate Order.

B. Fact discovery shall commence on all Initial Bellwether Discovery Cases 30 days after the certification of substantial completion of the following discovery by the Defendant:

1. the complete NDA file;

2. all relevant adverse-event data;

3. the production of the custodial files of at least 75% of the agreed (or ordered) custodians.

C. Fact discovery shall consist of:

1. the deposition of the Plaintiff,

2. the deposition(s) of all medical providers that prescribed Tepezza to the Plaintiff,

3. the deposition of one medical provider that diagnosed or treated the Plaintiff's alleged Tepezza-related injuries, and

4. the deposition of one case-specific sales employee of Defendant that interacted with Plaintiff's treating and/or prescribing physicians.

D. Once fact discovery commences, the parties shall have 150 days to complete fact discovery on all six Initial Bellwether Discovery cases. The fact-discovery period may be extended only by agreement of the parties or with a showing of good cause to the Court that is specific to the case for which an extension is sought.

V. Motion practice on Initial Bellwether Discovery Cases

A. To the extent that Defendant elects to seek dismissal under Fed. R. Civ. P. 12(b)(6) as to any of the Initial Bellwether Discovery Cases, its deadline to do so will be 30 days after identification of the Initial Bellwether Discovery Cases. Discovery will proceed during the pendency of any such motion.

B. **Consolidated briefing for common issues.** To maximize efficiency and eliminate repetition, to the extent Defendant seeks dismissal of any of the claims alleged in an Initial Bellwether Discovery Case on a basis common to all of the cases, *e.g.*, preemption, Defendant will submit a consolidated motion and supporting memorandum as to any Initial Bellwether Discovery Case to which it argues that common basis applies.

C. **Individual briefing for case-specific issues.** To the extent Defendant seeks dismissal of any of the claims alleged in an Initial Bellwether Discovery Case on a basis that is not common to all of the cases, *e.g.*, under the

applicable state law, it will do so by separate motion and memorandum as to that Individual Bellwether Discovery Case.

D. Plaintiffs will have 45 days after the filing of any Rule 12(b)(6) motion to submit their consolidated response (as to any common issues) and individual responses (as to any case-specific issues).

E. Defendants will have 15 days after Plaintiffs responses to submit any reply memoranda.

VI. Selection of Initial Bellwether Trial Cases

A. Within 14 days after fact discovery has been completed for the six Initial Bellwether Discovery Cases, Plaintiffs' Co-Lead Counsel and Defendant's Counsel shall each simultaneously identify to one another one case as an Initial Bellwether Trial Case. Within seven days thereafter, the parties shall jointly notify the Court of the two Initial Bellwether Trial Cases that have been selected along with a memorandum not to exceed three pages for each party that identifies an additional case that should be selected by the Court as the third Initial Bellwether Trial Case. The memorandum shall explain how the case selected is representative of the body of then-filed cases and include any other information that the party believes will assist the Court in making the proper selection. The parties shall also include a separate memorandum not to exceed two pages that explains the order the party contends the cases should be tried in along with the supporting bases for that contention.

B. The Court will select the third Initial Bellwether Trial Case and shall determine the order in which the Initial Bellwether Trial Cases will be tried, based on the parties' submissions.

C. Deadlines related to additional fact discovery, experts, and *Daubert*/summary judgment briefing for Initial Bellwether Trial cases shall be imposed in a separate Order.

D. This Order may be modified or amended by the agreement of the parties or for good cause shown, after appropriate notice and opportunity to be heard is provided to the affected parties, when the Court finds the interests of justice dictates modification.

IT IS SO ORDERED.

Ordered this ____ day of _____, 2023.

_____
Thomas M. Durkin
United States District Judge

EXHIBIT 2

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEPEZZA safely and effectively. See full prescribing information for TEPEZZA.

TEPEZZA (teprotumumab-trbw) for injection, for intravenous use
Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	4/2023
Warnings, and Precautions,	
Hyperglycemia (5.3)	12/2022
Hearing Impairment Including Hearing Loss (5.4)	7/2023

----------INDICATIONS AND USAGE----------

TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease (1)

----------DOSAGE AND ADMINISTRATION----------

- Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (2.1)
- Administer TEPEZZA by intravenous infusion over 60 to 90 minutes (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For Injection: 500 mg lyophilized powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Infusion Reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)
- Exacerbation of Preexisting Inflammatory Bowel Disease (IBD): Monitor patients with preexisting IBD for flare of disease; discontinue TEPEZZA if IBD worsens (5.2)
- Hyperglycemia: Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA (5.3)
- Hearing Impairment Including Hearing Loss: TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence greater than 5%) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia, headache, weight decreased and nail disorder (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Females of Reproductive Potential: Appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of TEPEZZA is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks for 7 additional infusions.

2.2 Reconstitution and Preparation

Step 1: Calculate the dose (mg) and determine the number of vials needed for the 10 or 20 mg/kg dosage based on patient weight. Each TEPEZZA vial contains 500 mg of the teprotumumab antibody.

Step 2: Using appropriate aseptic technique, reconstitute each TEPEZZA vial with 10 mL of Sterile Water for Injection, USP. Ensure that the stream of diluent is not directed onto the lyophilized powder, which has a cake-like appearance. Do not shake, but gently swirl the solution by rotating the vial until the lyophilized powder is dissolved. The reconstituted solution has a volume of 10.5 mL. Withdraw 10.5 mL of reconstituted solution to obtain 500 mg. After reconstitution, the final concentration is 47.6 mg/mL.

Step 3: The reconstituted TEPEZZA solution must be further diluted in 0.9% Sodium Chloride Injection, USP prior to infusion. To maintain a constant volume in the infusion bag, a sterile syringe and needle should be used to remove the volume equivalent to the amount of the reconstituted TEPEZZA solution to be placed into the infusion bag. Discard the 0.9% Sodium Chloride, USP volume withdrawn.

Step 4: Withdraw the required volume from the reconstituted TEPEZZA vial(s) based on the patient's weight (in kg) and transfer into an intravenous bag containing 0.9% Sodium Chloride Solution, USP to prepare a diluted solution with a total volume of 100 mL (for less than 1800 mg dose) or 250 mL (for 1800 mg and greater dose). Mix diluted solution by gentle inversion. Do not shake.

The product does not contain any preservative. The combined storage time of reconstituted TEPEZZA solution in the vial and the diluted solution in the infusion bag containing 0.9% Sodium Chloride Injection, USP is a total of 4 hours at room temperature 20°C to 25°C (68°F to 77°F) or up to 48 hours under refrigerated conditions 2°C to 8°C (36°F to 46°F) protected from light. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Upon reconstitution, TEPEZZA is a colorless or slightly brown, clear to opalescent solution which is free of foreign particulate matter. Discard the solution if any particulate matter or discoloration are observed.

Do not freeze the reconstituted or diluted solution.

Discard vial(s) and all unused contents.

No incompatibilities between TEPEZZA and polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) or polyolefin (PO) bags and intravenous administration sets have been observed.

2.3 Administration

Administer the diluted solution intravenously over 90 minutes for the first two infusions. If well tolerated, the minimum time for subsequent infusions can be reduced to 60 minutes. If not well tolerated, the minimum time for subsequent infusions should remain at 90 minutes.

Do not administer as an intravenous push or bolus. TEPEZZA should not be infused concomitantly with other agents.

3 DOSAGE FORMS AND STRENGTHS

For injection (intravenous infusion): 500 mg of teprotumumab as a white to off-white lyophilized powder in a single-dose vial for reconstitution and dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

5.2 Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

5.3 Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Assess patients for elevated blood glucose and symptoms of hyperglycemia prior to infusion and continue to monitor while on treatment with TEPEZZA. Ensure patients with hyperglycemia or pre-existing diabetes are under appropriate glycemic control before and while receiving TEPEZZA.

5.4 Hearing Impairment Including Hearing Loss

TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Assess patients' hearing before, during, and after treatment with TEPEZZA and consider the benefit-risk of treatment with patients.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Exacerbation of Preexisting Inflammatory Bowel Disease *[see Warnings and Precautions (5.2)]*
- Hyperglycemia *[see Warnings and Precautions (5.3)]*
- Hearing Impairment Including Hearing Loss *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1. In addition, menstrual disorders (amenorrhea, metrorrhagia, dysmenorrhea) were reported in approximately 23% (5 of 22 patients) of menstruating women treated with TEPEZZA compared to 4% (1 of 25 patients) treated with placebo in the clinical trials.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0
Weight decreased	5 (6%)	0
Nail disorder[d]	4 (5%)	0

[a] Fatigue includes asthenia
[b] Hyperglycemia includes blood glucose increase
[c] Hearing impairment including hearing loss (deafness, including sensorineural deafness, eustachian tube dysfunction, hyperacusis, hypoacusis, autophony and tinnitus)
[d] Nail disorder (includes nail discoloration, nail disorder and onychoclasis)

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEPEZZA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolism and Nutrition Disorders: diabetic ketoacidosis, hyperosmolar hyperglycemic state (HHS)
Otologic: severe hearing impairment including hearing loss, which in some cases may be permanent

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor 1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There are insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss *[see Data]*. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA. If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose (MRHD) based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

8.2 Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breast-fed infant or the effects on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

10 OVERDOSAGE

No information is available for patients who have received an overdosage.

11 DESCRIPTION

Teprotumumab-trbw, an insulin-like growth factor-1 receptor inhibitor (IGF-1R), is a fully human IgG1 monoclonal antibody produced in Chinese hamster ovary (CHO-DG44) cells. It has a molecular weight of approximately 148 kilodaltons.

TEPEZZA (teprotumumab-trbw) for injection is supplied as a sterile, preservative-free, white to off-white, lyophilized powder for intravenous infusion. Each single-dose vial contains 500 mg of teprotumumab-trbw, L-histidine (7.45 mg), L-histidine hydrochloride monohydrate (31.8 mg), polysorbate 20 (1 mg), and trehalose dihydrate (946 mg). After reconstitution with 10 mL of Sterile Water for Injection, USP, the final concentration is 47.6 mg/mL with a pH of 5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Teprotumumab-trbw's mechanism of action in patients with Thyroid Eye Disease has not been fully characterized. Teprotumumab-trbw binds to IGF-1R and blocks its activation and signaling.

12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with teprotumumab-trbw.

12.3 Pharmacokinetics

The pharmacokinetics of teprotumumab-trbw was described by a two compartment population PK model based on data from 40 patients with Thyroid Eye Disease receiving an initial intravenous infusion of 10 mg/kg, followed by infusions of 20 mg/kg TEPEZZA every 3 weeks in one clinical trial. Following this regimen, the mean (± standard deviation) estimates for steady-state area under the concentration curve (AUC), peak (Cmax), and trough (Ctrough) concentrations of teprotumumab-trbw were 138 (± 34) mg•hr/mL, 632 (± 139) mcg/mL, and 176 (± 56) mcg/mL, respectively.

Distribution
Following the recommended TEPEZZA dosing regimen, the population PK estimated mean (± standard deviation) for central and peripheral volume of distribution of teprotumumab-trbw were 3.26 (±0.87) L and 4.32 (± 0.67) L, respectively. The mean (± standard deviation) estimated inter-compartment clearance was 0.74 (± 0.16) L/day.

Elimination
Following the recommended TEPEZZA dosing regimen, the population PK estimated mean (± standard deviation) for the clearance of teprotumumab-trbw was 0.27 (± 0.08) L/day and for the elimination half-life was 20 (± 5) days.

Metabolism
Metabolism of teprotumumab-trbw has not been fully characterized. However, teprotumumab-trbw is expected to undergo metabolism via proteolysis.

Specific Populations
No clinically significant differences in the pharmacokinetics of teprotumumab-trbw were observed following administration of TEPEZZA based on patient's age (18-80 years), gender, race/ethnicity (103 White, 10 Black, and 3 Asian), weight (46-169 kg), mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min estimated by Cockcroft-Gault Equation), bilirubin levels (2.7-24.3 mcmol/L), aspartate aminotransferase (AST) levels (11-221 U/L), or alanine aminotransferase (ALT) levels (7-174 U/L). The effect of hepatic impairment on the pharmacokinetics of teprotumumab-trbw is unknown.

Drug Interactions
No studies evaluating the drug interaction potential of TEPEZZA have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
The carcinogenic potential of TEPEZZA has not been evaluated in long-term animal studies.

Mutagenesis
The genotoxic potential of TEPEZZA has not been evaluated.

Impairment of Fertility
Fertility studies have not been performed with TEPEZZA.

14 CLINICAL STUDIES

TEPEZZA was evaluated in 2 randomized, double-masked, placebo-controlled studies in 171 patients with Thyroid Eye Disease: Study 1 (NCT01868997) and Study 2 (NCT03298867). Patients were randomized to receive TEPEZZA or placebo in a 1:1 ratio. Patients were given intravenous infusions (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) every 3 weeks for a total of 8 infusions. Patients had a clinical diagnosis of Thyroid Eye Disease with symptoms and were euthyroid or had thyroxine and free triiodothyronine levels less than 50% above or below normal limits. Prior surgical treatment for Thyroid Eye Disease was not permitted. Proptosis ranged from 16 to 33 mm and 125 patients (73%) had diplopia at baseline.

A total of 84 patients were randomized to TEPEZZA and 87 patients were randomized to placebo. The median age was 52 years (range 20 to 79 years), 86% were White, 9% were Black or African-American, 4% were Asian and 1% identified as Other. The majority (73%) were female. At baseline, 27% of patients were smokers.

The proptosis responder rate at week 24 was defined as the percentage of patients with ≥2 mm reduction in proptosis in the study eye from baseline, without deterioration in the non-study eye (≥2 mm increase) in proptosis. Additional evaluations included signs and symptoms of Thyroid Eye Disease including pain, gaze evoked orbital pain, swelling, eyelid erythema, redness, chemosis, inflammation, clinical activity score and assessments of functional vision and patient appearance. Results for proptosis are found in Table 2.

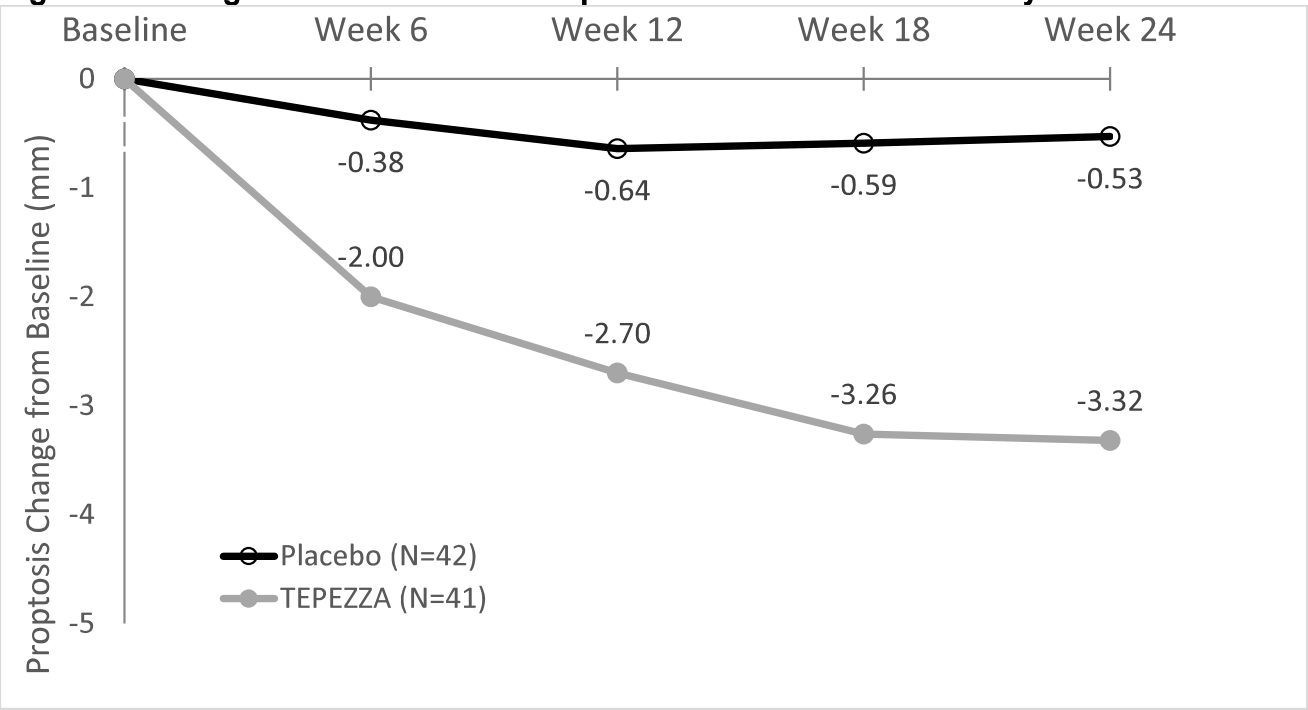
Table 2. Efficacy Results in Patients with Thyroid Eye Disease in Study 1 and 2

	Study 1			Study 2		
	Teprotumumab (N=42)	Placebo (N=45)	Difference (95% CI)	Teprotumumab (N=41)	Placebo (N=42)	Difference (95% CI)
Proptosis responder rate at week 24, % (n) [1]	71% (30)	20% (9)	51% (33, 69)	83% (34)	10% (4)	73% (59, 88)
Proptosis (mm) average change from baseline through week 24, LS Mean (SE) [2]	-2.5 (0.2)	-0.2 (0.2)	-2.3 (-2.8, -1.8)	-2.8 (0.2)	-0.5 (0.2)	-2.3 (-2.8, -1.8)

[1] Difference and its corresponding 95% Confidence Interval (CI) is based on a weighted average of the difference within each randomization stratum (tobacco user, tobacco non-use) using CMH weights.
[2] Results were obtained from an MMRM with an unstructured covariance matrix and including treatment, smoking status, baseline value, visit, treatment by visit, and visit by baseline value interaction as fixed effects. A change from Baseline of 0 was imputed at the first post-Baseline visit for any subject without a post-Baseline value.

In Study 2, improvement of proptosis as measured by mean change from Baseline was observed as early as 6 weeks and continued to improve through week 24 as shown in Figure 1. Similar results were seen in Study 1.

Figure 1. Change from Baseline in Proptosis over 24 Weeks in Study 2



P<0.01 at each timepoint

TEPEZZA also led to improvement in the less severely impacted "fellow" eye.

Diplopia (double vision) was evaluated in a subgroup of patients that had diplopia at baseline in Study 1 and 2. Results are shown in Table 3.

Table 3. Diplopia in Patients with Thyroid Eye Disease in Study 1 and 2

Parameter	TEPEZZA (n=66)	Placebo (n=59)
Diplopia Responder rate[a] at week 24, % (n)	53% (35)	25% (15)

P<0.01

[a] Diplopia was evaluated on a 4-point scale where scores ranged from 0 for no diplopia to 3 for constant diplopia. A diplopia responder was defined as a patient with baseline diplopia >0 and a score of 0 at week 24.

Following discontinuation of treatment in Study 1, 53% of patients (16 of 30 patients) who were proptosis responders at week 24 maintained proptosis response 51 weeks after the last TEPEZZA infusion. 67% of patients (12 of 18) who were diplopia responders at week 24 maintained diplopia response 51 weeks after the last TEPEZZA infusion.

Subgroups

Examination of age and gender subgroups did not identify differences in response to TEPEZZA among these subgroups. Reduction in proptosis was similar between smokers and non-smokers in both studies.

16 HOW SUPPLIED/STORAGE AND HANDLING

TEPEZZA (teprotumumab-trbw) for injection is a sterile, preservative-free, white to off-white lyophilized powder available as follows:

Carton containing one 500 mg single-dose vial	NDC 75987-130-15

Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton until time of use to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

- Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
- Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-related reactions

- Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Preexisting Inflammatory Bowel Disease

- Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

- Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control measures including medications as appropriate. Encourage compliance with glycemic control.

Hearing Impairment Including Hearing Loss

- Advise patients that TEPEZZA may cause severe hearing impairment including hearing loss, which in some cases may be permanent. Instruct patients to contact their healthcare provider if they experience any signs or symptoms of hearing impairment or any changes in hearing.

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