CLOSER LOOK

FDA Advisory Committee Meeting for Novo Nordisk's Xultophy (insulin degludec/ liraglutide)

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Executive Highlights

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee held a meeting today to discuss Novo Nordisk's exciting basal insulin/GLP-1 agonist combination Xultophy (insulin degludec/liraglutide). See below for our top five highlights from the meeting, followed by detailed coverage of the Open Public Hearing and panelists' comments on the voting question.

1. The meeting ended with a unanimous 16-0 vote in favor of approval - a testament to Xultophy's extremely compelling risk/benefit profile.

2. In the absence of any major safety signals, most of the FDA's concerns about Xultophy centered around dosing considerations and the generalizability of the phase 3 efficacy data.

3. The panel took a fairly conservative view of the potential patient population for Xultophy, favoring those already treated with one of the components. We were somewhat disappointed by this, though basically just want to see it on the US market.

4. Despite the dosing and generalizability concerns, panelists acknowledged that the single injection aspect of the combination is huge and could encourage greater patient acceptance than attempting to initiate two separate injectable therapies.

5. The 13 presentations at the Open Public Hearing constituted a ringing endorsement of Xultophy.

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Top Five Highlights

1. The meeting ended with a unanimous 16-0 vote in favor of approval - a testament to Xultophy's extremely compelling risk/benefit profile. We had expected that the verdict would be favorable for Xultophy given its clear efficacy and lack of any significant new safety concerns, but this unanimous stamp of approval is very encouraging. We would be shocked at this point if the FDA did not follow the committee's recommendation for approval, though it has a number of questions to consider related to the label. Many of the panelists qualified their yes votes with caveats about the ideal target population for Xultophy and/or concerns about dosing and the flaws of the phase 3 trial program. It troubled us a bit that many doctors who were characterizing "ideal" patient populations were not really clinicians and were doing so based on impressions of A1c absent additional information on hypoglycemia, time in target zone, quality of life, etc. We would therefore not be surprised to see fairly detailed guidance on dosing and different recommendations related to different patient populations in the label. Based on today's discussion, it also seems possible that the FDA might approve Xultophy only for patients already treated with one of its components, though we still see this as unlikely - see below for more on this.

2. In the absence of any major safety signals, most of the FDA's concerns about Xultophy centered around dosing considerations and the generalizability of the phase 3 efficacy data. Many of these issues were also raised in the briefing documents released before the meeting. For one, the FDA took issue with the cap on insulin dosing in the DUAL II study comparing Xultophy to Tresiba (insulin degludec), suggesting that it may have biased the efficacy results in favor of the combination. The Agency also expressed concerns that patients in the insulin comparator arms of DUAL I and DUAL V (in which insulin dosing was not capped) had not reached a stable dose of insulin by the end of the 26-week treatment period, likely due to a conservative titration algorithm and low glycemic targets. The FDA therefore suggested that the final A1c in these groups may have been misleadingly high, again biasing the efficacy results in favor of Xultophy. Novo Nordisk countered that A1c was stable in both groups after ~week 12 and that continued titration of basal insulin did not produce any additional improvements in glycemic control. The FDA also raised concerns about the potential for patients with low insulin requirements to receive overly low doses of liraglutide that carry a risk of side effects without contributing to glycemic control. This looks to be relevant primarily for patients adding Xultophy to oral drugs: in trials in that population, 27% of patients were on a dose of liraglutide <0.6 mg (the approved starting dose for the standalone product) at the end of the study. Several panelists also questioned the lack of units for Xultophy doses (e.g., a dose of 50 units insulin degludec/1.8 mg liraglutide is simply "50") and raised concerns that the maximum of 50 units of insulin will not be appropriate for many patients with severe insulin resistance. We agree that having "no" units is a bit odd - our team tonight thought of three potential units that could be used, including "zolts" as the favorite. "How many zolts is she taking?" Incs was another possible unit (short for increments) as well as us for units.

3. The panel took a fairly conservative view of the potential patient population for Xultophy. Many panelists felt that the combination should only be used in patients already on a GLP-1 agonist, a basal insulin, or both. We felt this was short-sighted. Some panelists felt that optimal diabetes management could be achieved through individual titration of the two components and initiation of Xultophy only if the final optimal ratio of basal insulin to GLP-1 agonist matched the fixed ratio of the combination product. From our view, this is missing the forest for the trees as it creates a major pain to get two pens, titrate separately, etc - it could be done if really needed but our preference would be one titration. Dr. Kenneth Burman (MedStar Georgetown University Hospital, Washington, DC) and others noted that switching from standalone liraglutide or insulin degludec to Xultophy involves a reduction in the dose of liraglutide or insulin degludec at initiation before the combination product is titrated up. Chairperson Dr. Robert Smith (Brown University, Providence, RI) felt that the minor increase in fasting glucose for 1-3 weeks from this minor initial dose reduction has few serious clinical risks. Patient representative Ms. Barbara Berney (Rockford, IL) told her compelling story of quitting insulin therapy after gaining ~30 pounds in two months and suggested that Xultophy could be a good option for patients who are similarly reluctant to initiate insulin therapy due to weight gain concerns. In terms of A1c, many panelists felt that Xultophy could be appropriate for many patients with an A1c 7%-9% or 7.5%-10%, whereas patients with a higher A1c would generally require higher insulin doses than the maximum 50 units offered by Xultophy. We thought the focus was too much on A1c in these conversations without as much acknowledgement about "quality" of glycemic profile.

4. Despite these concerns, panelists acknowledged that the single injection aspect of the combination is huge and could encourage greater patient acceptance than attempting to initiate two separate injectable therapies. Ultimately, the panel felt that there was not enough clinical data on the glycemic impact of switching from a GLP-1 agonist or a basal insulin to Xultophy but that the switch from GLP-1 agonist to Xultophy was likely the safer of the two. We were encouraged by the unanimous vote in support of a favorable risk/benefit profile for the product, and we hope that the FDA ultimately approves Xultophy for a broad type 2 diabetes indication, not just for patients who are on at least one of the component agents. We see Xultophy as a promising first injectable therapy overall. Earlier use of a combination product represents a more aggressive approach to type 2 diabetes management that could even potentially have benefits in terms of preserving beta cell function.

5. The 13 presentations at the Open Public Hearing constituted a ringing endorsement of Xultophy. Patients, providers, and patient advocates discussed the challenges of daily diabetes management and Xultophy's potential to improve outcomes by promoting better adherence. See below for more detailed

coverage of these moving and informative presentations - Ms. Kelly Close of the diaTribe Foundation opened the OPH and Dr. Bob Ratner, Chief Scientific Officer of the ADA, closed it.

Detailed Discussion and Commentary

Open Public Hearing

- **Our very own Ms. Kelly Close provided compelling commentary on the potential for Xultophy to optimize the lives of people with diabetes and their healthcare providers through its simple, patient-centered design.** Ms. Close underscored the value of drugs that fit into patients' lives and providers' workflow, emphasizing her belief that Xultophy has a better chance than the current standard of care to achieve this goal. She also urged panelists to consider the impact of drugs on quality of life - "RCTs are so valuable, but from a patient perspective we want to know what real life will be like." She noted that Xultophy's promise of less hypoglycemia, less worry about hypoglycemia, and less weight gain can indeed improve quality of life and make it easier for patients to take the next step in their diabetes management successfully. In addition, Ms. Close vehemently expressed the importance of access, stating that although access is not exactly the realm of the FDA, if drug are approved but not covered, they might as well not be approved. She posited that even savings from two co-pays to one could make a meaningful difference for some patients. According to Ms. Close, if Xultophy is approved and affordable, it can help achieve what we all want for patients: better health and a better quality of life.
- **Patient Mr. Christopher Tasik (travel paid for by Novo Nordisk) spoke from personal experience about the daily management of type 2 diabetes and the need for improved therapies.** He emphasized that his day-to-day experience as a patient with diabetes is very different from the perspective of the scientific community - "the scientific community measures success from trials, but we add the extra measure of less pain, less burden, and for some less fear [of injections] to get to the same goal." He argued that Xultophy represents an exciting new opportunity for better glycemic control; for patients like him who are already treated with the two components separately, it also represents 365 fewer injections per year. Mr. Tassick celebrated the advances in diabetes therapies and technologies over the past 20 years that have made diabetes much more manageable and argued that we need continued R&D efforts to ensure that this trend continues. He also spoke about affordability and noted that his deductible was over $6,000 and co-pays did not count (!) toward it - his wife works for UBS, he shared, where PPOs are no longer available.
- **Dr. Stanley Schwartz, representing AACE, suggested that GLP-1 agonist/basal insulin fixed-ratio combinations offer the ability to treat more aspects of the underlying pathophysiology of diabetes with fewer medications.** He emphasized that both patients and physicians need more choices and pointed out the logical benefits of GLP-1 agonist/basal insulin combinations, including the potential to decrease basal insulin doses, reduce risk of hypoglycemia, avoid weight gain, and reduce glycemic variability. He also expressed the hope that the combination product can reduce medication burden and cost for patients. Dr. Schwartz noted that many of these benefits track well with the goals put forth by the AACE/ACE principle of diabetes management, which emphasizes aiming for the lowest target A1c possible while avoiding hypoglycemia and weight gain and using the least number of agents to treat the most number of mechanisms driving hyperglycemia in type 2 diabetes. He especially emphasized the importance of the reduced risk of hypoglycemia with Xultophy and linked hypoglycemia to acute cardiovascular events. Turning to AACE/ACE's comprehensive stepwise treatment algorithm, Dr. Schwartz concluded, "Basically, we don't want to use insulin until we have to, and if we have to, we're going to use a combination with insulin to minimize the cost and complications of diabetes to provide the greatest benefit to our patients."
- **Ms. Lizmari Collazo delivered a passionate and moving presentation on her personal experience with type 2 diabetes, stressing the importance of multiple drug options for patients.** She explained how insulin carries a great deal of myth, fear, and stigma, causing patients - including her own father - to delay insulin therapy and jeopardize their health. To that end, she

urged the panel to approve Xultophy to provide patients with more possibilities that do not carry the same risk of hypoglycemia, weight gain, and dosing confusion. She also asked panelists to consider the psychosocial effects of drugs and the importance of approving drugs that help patients take ownership of their wellbeing rather than feel like they are sacrificing their health and independence.

- **Endocrinologist Dr. Paul Norwood (travel paid for by Novo Nordisk) discussed Xultophy's appeal for providers like him who care for a large number of patients with type 2 diabetes.** He explained that he was initially skeptical about the benefits of a fixed-ratio GLP-1 agonist/basal insulin combination relative to treatment with the two components separately, but he now believes he has been proven wrong - "this stuff works." He highlighted reductions in insulin dose, hypoglycemia, and body weight as key advantages for Xultophy compared to basal insulin. Interestingly, he also noted that he has not seen a single patient referred to him who was taking both a GLP-1 agonist and basal insulin and suggested that the combination might spur increased use of GLP-1 agonists among primary care providers. While he acknowledged that Xultophy would not be appropriate for patients with very high insulin requirements, he believes that the majority of those with insulin requirements of 70 units or less will be able to reach target with metformin, Xultophy, and an SGLT-2 inhibitor.
- **Patient advocate and former Miss America Dr. Nicole Johnson advocated for Xultophy's approval, suggesting that the combination could reduce the confusion and hesitance patients often feel when faced with initiation or intensification of therapy.** She characterized Xultophy as a "gift" that could "aid individuals with type 2 diabetes who feel helpless, feel disempowered, have been told they're in a poor state of health, and are worried about their futures." She pointed out that these patients are often intimidated by the prospect of initiating a single diabetes product, and this is only exacerbated as patients move to multiple products. As a combination product, Xultophy could reduce these feelings of confusion and intimidation for many patients. Beyond patient satisfaction, Dr. Johnson also asserted that the combination product could be safer for some patients who might confuse multiple different injectable products, potentially leading to dosing errors. Additionally, Dr. Johnson highlighted Xultophy's effect on body weight as one of its most exciting aspects for many patients. From a public health perspective, Dr. Johnson suggested that Xultophy's weight loss benefit could help turn the tide of rising prediabetes rates. Finally, Dr. Johnson ended on a personal note, stating her belief that Xultophy could improve her father's quality of life. As a patient with type 1 diabetes, she has also used a GLP-1 agonist in combination with insulin herself for many years and she underscored the feeling of strength, control, and improved quality of life this has given her.
- **diaTribe's Ms. Nicole Kofman shared valuable commentary from Ms. Joyce Gresko, who was unable to attend the meeting due to a last-minute conflict.** In her written statement, Ms. Gresko drew from her personal experience as a healthcare attorney and patient, emphasizing Xultophy's ability to meet patients' needs and help them be successful in their diabetes management. She highlighted Xultophy's patient-centered benefits as a combination drug, such as "fewer pokes", a single co-pay, and a lower chance of forgetting medications - "anything that facilitates adherence is a step in the right direction," she stated. Ms. Gresko ended her statement by urging the FDA to not only approve Xultophy, but also ensure access through inclusion in drug formularies.
- **Dr. Steve Edelman (UCSD, San Diego, CA) discussed Xultophy's potential to help fill the unmet need for new type 2 diabetes therapies that improve glycemic control and adherence.** He emphasized that despite the large number of approved agents for type 2 diabetes, average glycemic control has remained flat for the past ten years and the number of people with an A1c >9% has actually increased. In his view, "something is seriously wrong with this picture." Dr. Edelman pointed to the "shockingly poor" adherence to current therapies as a major factor behind these poor outcomes and argued that any therapy that is effective, safe, and easy to administer will at least make a dent in the problem. He described Xultophy as a combination of two agents that have

withstood the test of time and a product with significant potential to improve diabetes care at the community level.

- **Mr. Brian Cohen shared his personal experience using basal insulin and GLP-1 agonists as a patient with type 2 diabetes.** In the 11 years since his type 2 diabetes diagnosis, Mr. Cohen has tried many diabetes drugs from a variety of classes, including the GLP-1 agonist Victoza (liraglutide). He shared that, while the GLP-1 agonist was able to manage his postprandial glucose to some extent, he still struggled with high fasting blood glucose. As a result, his physician chose to initiate a basal insulin. At the time, GLP-1 agonists were not approved for use with basal insulins and thus Mr. Cohen had to immediately move to basal-bolus therapy with 4-5 injections per day. He emphasized that he would have loved to intensify to Xultophy instead, which would have let him control both his fasting glucose and his post-meal glucose without carb counting or complicated dosing of bolus insulin. Furthermore, Mr. Cohen actually had to fight his physicians' reluctance to prescribe him insulin and eventually resorted to purchasing it over-the-counter at his local Walmart. He suggested that Xultophy could help ease this resistance to insulin therapy from both providers and patients and, in doing so, improve the effectiveness of diabetes management, reduce the hurdles in moving from oral medications to insulin, and improve the quality of life for patients from a cost and adherence perspective.
- **Our own Ms. Ava Runge (Close Concerns, San Francisco, CA) shared data from dQ&A, the diabetes market research company to illustrate Xultophy's ability to address many of the key barriers to basal insulin intensification.** A survey of approximately 5,000 people with type 2 diabetes found that only 12% of patients on basal insulin, and only 22% of those with an A1c >9%, have had a conversation with their physician about adding mealtime insulin. The most frequently cited barriers to intensification were more hassle, difficulty dosing/calculating carbs, cost, hypoglycemia, and weight gain. Ms. Runge argued that Xultophy can address all of these concerns: it does not increase injection burden for patients already on basal insulin, it does not require carb counting, it allows patients to pay a single copay instead of two, and it carries a lower risk of hypoglycemia and weight gain than basal insulin alone. She described it as potentially a real game changer for patients with type 2 diabetes, "who are people before anything else."
- **Our very own Ms. Emily Regier (Close Concerns, San Francisco, CA) discussed the enthusiasm and praise GLP-1 agonist/basal insulin fixed-ratio combinations have generated on the conference circuit.** She shared that Close Concerns has reported on around 50 talks at 17 different scientific meetings on the topic of these combination products and emphasized the compelling nature of the phase 3 data supporting them. She quoted several key opinion leaders praising these combinations and their versatility ("the modern equivalent of basal-plus therapy," "the most effective way to treat type 2 diabetes, bar none," "if I only get one shot on goal, I do think this is the single best shot we have. Pun not intended"). Ms. Regier's talk offered an opportunity for the panel to consider opinions from experts who were not able to speak at the Advisory Committee meeting themselves.
- **Mr. Douglas Herring shared his personal experience participating in a Xultophy trial, highlighting the transformative effect it had on his diabetes management and life overall.** He detailed how he struggled for years to manage his diet and physical activity, as his job as a tow truck driver made it challenging to integrate healthy habits into his daily routine. However, during his time in the Xultophy trial, Mr. Herring was able to lose 60 pounds and reduce his A1c from 9% to 5%. With his blood glucose under better control, he suddenly discovered he had much more energy to exercise - "I didn't realize that diabetes had such an impact on me until I started to feel so much better." Mr. Herring concluded with his hope that doctors will soon be able to prescribe Xultophy to other patients with diabetes and help give them their lives back as well.
- **Dr. Robert Ratner (ADA, Alexandria, VA) discussed the need for more treatment options to help achieve the goals of intensive glycemic control, individualization of therapy, and good adherence.** He explained that the ADA standards of medical care for type 2 diabetes emphasize the importance of a patient-centered approach to treatment that is focused on

choice, flexibility, and individualization - "one size definitely does not fit all." He emphasized that type 2 diabetes is a progressive, multifaceted disease that likely requires earlier, more aggressive combination therapy than is typical in current practice. In his discussion of Xultophy, Dr. Ratner focused on its potential to improve adherence by reducing the number of injections and copays, quipping that a medication will always be ineffective if it is never purchased or never leaves the bottle.

Commentary from Voting Committee Members

Following the final panel vote, each panelist was allowed a few minutes to explain his or her decision. Included below are summaries of each statement, arranged in alphabetical order by speakers' last names. The panel unanimously voted in favor of approval, though some raised caveats in their comments.

- **Patient Representative Ms. Barbara Berney shared her belief that Xultophy would be another great addition to the "arsenal" of diabetes therapies, and would aid in compliance and the simplification of patients' lives.**
- **Dr. Daniel Budnitz (CDC, Atlanta, GA) suggested that Xultophy should be approved based on its potential to reduce medication burden and needle sticks in the patients already taking both basal insulin and GLP-1 agonists separately.** That said, Dr. Budnitz noted that some patients might take Xultophy who could be optimally managed with just one of the component agents or with a different ratio of the component agents. Dr. Budnitz also suggested that some sort of unit be included to reduce confusions in dosing the combination product.
- **Dr. Kenneth Burman (MedStar Georgetown University Hospital, Washington, DC) stated his belief that it will be most appropriate to use Xultophy in uncontrolled type 2 patients who are already taking basal insulin or a GLP-1 agonist.** He also noted that a combination product is a "double edged sword" with both advantages and disadvantages: greater adherence, decreased cost, A1c benefit, and fewer injections vs. incremental dosing schedule, possibility for medication error, maximum dose of 50, and some missing data.
- **Dr. David Cooke (Johns Hopkins University, Baltimore, MD) supported approval for all of the groups studied in the phase 3 program - a wider population than many of the other panelists.** He agreed that it is less clear how to initiate Xultophy in patients not on either component but suggested that is something that will be determined over time. He also suggested that there was no need for additional post-marketing studies, as the phase 3 data was sufficient to prove that Xultophy is safe and efficacious.
- **Dr. Brendan Everett (Brigham and Women's Hospital, Boston, MA) found the efficacy data for Xultophy vs. insulin compelling enough for a yes vote but raised several additional concerns.** He suggested that additional clinical trial data would have been helpful and hoped to see some of the missing data filled in with the full presentation of the LEADER CVOT results for Victoza at ADA 2016 in June. He also expressed reservations about the imbalances in dose titration between Xultophy and insulin comparators. In terms of the patient population, he felt that Xultophy should be limited to patients already on at least one of the two components, with a preference for patients on a GLP-1 agonist over patients on basal insulin. Dr. Everett also called for a post-marketing study to better understand the next clinical steps for patients who are not adequately controlled on the maximum dose of Xultophy.
- **Dr. Marie Gelato (Stony Brook University, Stony Brook, NY) noted that she was impressed by Xultophy's demonstrated A1c benefit versus insulin degludec and liraglutide and suggested that it could be used for patients who have failed orals, insulin, or GLP-1 agonists.** She suggested that it is going to take clinician and patient experience to determine the best use of the drug going forward. Like many panelists, she highlighted the value of Xultophy as another drug in the tool kit - "diabetes is a tough disease and we need all of the things we can muster to get it under good control."

- **Consumer representative Ms. Diana Hallare (Visalia, CA) cited the stabilization rate, low side effects, efficacy data, weight loss, and decrease in systolic blood pressure as main factors contributing to her vote in favor of approval.** In addition, she suggested that the lower rate of hypoglycemia and improvement in quality of life will contribute to better adherence to the medication.
- **Dr. Timothy Lesar (Albany Medical Center, Albany, NY) agreed with the other panelists that the patient satisfaction, safety, and efficacy results outweigh the concerns about data and adverse events.** He noted that it might be difficult to prescribe the drug using electronic prescription ordering systems due to the lack of dose units and stated that it will be important for patients and caregivers to understand the nuances of combination therapy.
- **Dr. Steven Meisel (Fairview Health Services, Minneapolis, MN) suggested that Xultophy offers more value as a third-line treatment than a second-line treatment.** He also called for clearer guidelines about the patients for whom the combination is not appropriate (such as those with high insulin requirements) and emphasized the need for greater clarity about the dosing units and the fact that the product includes two separate drugs. He also raised the issue of an imbalance in skin cancer seen with Xultophy in clinical trials, which did not come up at all during the day's discussion. Dr. Meisel agreed with Novo Nordisk that there is no plausible mechanism linking Xultophy with an increased risk of skin cancer but argued that "that doesn't mean there isn't an implausible mechanism."
- **Dr. Martha Nason (NIH, Bethesda, MD) described the phase 3 data for Xultophy as convincing and suggested that patients already on an injectable drug would be the more obvious target population.** She deferred to her clinical colleagues on the exact details of the indication (her background is in statistics) but suggested that there is a clearer role for the product as a means to intensify basal insulin or GLP-1 agonist therapy rather than as a first injectable.
- **Dr. James Neaton (University of Minnesota, Minneapolis, MN) argued that the phase 3 program established that Xultophy's benefits exceeded its risks but echoed the FDA's concerns about the external validity of the studies.** He particularly criticized Novo Nordisk for the missing data from patients who withdrew from the trials and for their use of a "titration committee" to titrate insulin doses.
- **Dr. Michael Reed (Rainbow Babies and Children's Hospital, Cleveland, OH) found the pharmaceutical rationale for Xultophy compelling enough to vote for approval, though he raised the question of how the product might fit into the diabetes treatment paradigm moving forward.** He suggested that it was fairly clear how Xultophy might fit into the current treatment paradigm, but questioned how its positioning might change in the future. Ultimately, he felt it will be up to endocrinologists and diabetologists to clarify this.
- **Dr. Robert Smith (Brown University, Providence, RI) described Xultophy as a useful treatment option that meets an important need but raised several issues related to dosing and the label.** He encouraged the FDA to provide guidance about dosing for patients switching to Xultophy from insulin and urged Novo Nordisk to conduct labeling comprehension studies to ensure that patients understand the correct dosing. He also advocated for post-marketing assessment (through observational databases or ideally a dedicated study) to identify common characteristics of the patients who do not respond to Xultophy.
- **Dr. Charles Stanley (University of Pennsylvania, Philadelphia, PA) was particularly impressed with Xultophy's potential to normalize fasting glucose and A1c, in contrast to many new diabetes drugs that only lower A1c by ~1%.** He felt that Xultophy will clearly serve as an appropriate add-on to basal insulin or GLP-1 agonist monotherapy. Notably, Dr. Stanley also felt that Xultophy could be an appropriate second-line option after metformin, though he acknowledged that it may take some experience for physicians to get used to this concept.

- **Dr. Peter Wilson (Emory University, Atlanta, GA) stated that while he supports Xultophy's approval, he believes there are some key gaps and unanswered questions**. His main concerns were the need for longer term data to confirm A1c benefit and better determine the weight effect. Dr. Wilson also expressed concern about Xultophy's utility in patients with very high BMIs, who might require >50 units of insulin shortly after initiation. To that end, he advocated for a post-marketing project to evaluate the efficacy of Xultophy in various subpopulations.
- **Dr. Susan Yanovski (NIH, Bethesda, MD) believes Xultophy will be primarily useful in patients already on a GLP-1 agonist or basal insulin and has mixed feelings about its use in patients only on oral drugs.** She also expressed a desire to learn more about the effects with lower doses of the combination.

-- by Helen Gao, Emily Regier, Ava Runge, and Kelly Close