Case #7137 (12/30/2022)
Novartis Pharmaceuticals Corporation
Kisqali
Challenger: *Eli Lilly and Company*
Product Type: *Drugs/Health/Health Aids*
Issues: *Comparative Performance Claims; Establishment Claims; Express Claims; Health & Safety Claims; Implied Claims/Consumer Perception; Superiority Claims*
Disposition: *Modified / Discontinued*

BBB NATIONAL PROGRAMS

NATIONAL ADVERTISING DIVISION

ELI LILLY AND COMPANY,
Challenger,

NOVARTIS PHARMACEUTICAL CORPORATION
Advertiser.

Case No. 7137
Closed 12/30/2022

FINAL DECISION

- The degree of sophistication of the target audience is a factor in determining the reasonable message conveyed by the advertising.

- Where express or implied comparative performance claims are being made, head-to head studies of the products at issue constitute the most reliable and persuasive substantiation.

I. Basis of Inquiry

The advertising industry established the National Advertising Division (NAD) and the National Advertising Review Board (NARB) in 1971 as an independent system of self-regulation designed to build consumer trust in advertising. NAD reviews national advertising in all media in response to third-party challenges or through inquiries opened on its own initiative. Its decisions set consistent standards for advertising truth and accuracy, delivering meaningful protection to consumers and leveling the playing field for business. Challenger Eli Lilly ("Lilly" or "Challenger") challenged express and implied claims made by Advertiser Novartis Pharmaceutical ("Novartis" or "Advertiser") in physician and patient directed advertising for its breast cancer treatment drug, Kisqali. The following are representative of the claims that served as the basis for this inquiry:

A. Express Claims

- Live Longer with KISQALI - The Longest Overall Survival Data Ever Reported in HR+, HER2- mBC.

- "The longest survival data ever reported in HR+, HER2- mBC."
- "KISQALI - the longest median overall survival ever reported in HR+/HER2- mBC.

- "Kisqali has the longest median overall survival ever reported in HR+/HER2- metastatic breast cancer."
- "[O]nly drug in class with consistently proven overall survival benefit in HR+/HER2- metastatic breast cancer."

B. Implied Claims

- Kisqali® provides the longest overall survivability as compared to any other available treatment in the CDK4/6 inhibitor class generally and to Verzenio® specifically.
- Patients will live longer with Kisqali as compared to any other available treatment in the CDK4/6 inhibitor class generally and to Verzenio specifically.
- Kisqali provides superior survival benefits as compared to any other available treatment in the CDK4/6 inhibitor class generally and to Verzenio specifically.

II. Evidence Presented

The Challenger presented the following evidence: [1]

- Email correspondence between the parties in January and February of 2021 and June of 2022
- Samples of the challenged advertising on the patient facing section of the Kisqali website
- A video file of the challenged TV commercial "*Invest in your Future*"
- A flyer for Kisqali distributed at the ASW Annual General Meeting in June, 2022
- Novartis press release of June 3, 2022 announcing data from its MONALEESA-2 trial
- Results of the Challenger's MONARCH-2 study as presented on Lilly's website for its Verzenio drug
- Product specification annex for Verzenio
- A study entitled "*Effects of Patient Medication Requests on Physician Prescribing Behavior: Results of a Factorial Experiment*" published by the National Institutes of Health Med Care website.

The Advertiser presented the following evidence: [2]

- A PDF file of the Kisqali website with schematic overlay
- Story boards for the TV commercial *"Invest in Future"*
- Samples of HCP brochures for Kisqali
- Studies of 3 clinical trials for Kisqali published in the New England Journal of Medicine
- Conference presentation for Novartis MONALEESA-2 Trial
- Novartis press release of June 3, 2022 announcing data from its MONALEESA-2 trial
- Data summary of an online literature search of reported overall survival outcomes in clinical trials of HR+/HER2 metastatic breast cancer treatments

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[1] In its papers, the Challenger also included links to the following: October 2021 Lilly press release announcing FDA approval for Verzenio in high risk early breast cancer, the results of Lilly's MONARCH 2 study published in the Journal of the American Medical Association, and a Pfizer press release of June 4, 2022 announcing the results of its PALOMA -2 trial.

[2] In its papers, the Advertiser included links to the National Comprehensive Cancer Network's Clinical Practice Guidelines and to the FDA's Clinical Trial Endpoints for Approval of Cancer Drugs.

- An article entitled "*Kisqali Increases Overall survival in Advanced Breast Cancer Patients by 12 Months*" published in the European Pharmaceutical Review
- An article entitled "*The Rise of the Expert Patient in Cancer: From Backseat Passenger to Co-Navigator*" published in the Journal of Clinical Oncology
- Video file of a TV commercial for Verzenio "*Every Day Matters*"
- Abstract of the interim results of Lilly's MONARCH-3 trial published in the Annals of Oncology in September, 2022
- A 1965 article entitled "The Environment and Disease: Association or Causation?" published in the Proceedings of the Royal Society of Medicine

III. Decision

A. Background

The parties are global healthcare companies with pharmaceutical divisions that develop and manufacture drugs to treat metastatic breast cancer. Metastatic breast cancer, sometimes referred to as advanced or stage IV breast cancer, is cancer that has spread beyond the breast to other parts of the body. Roughly 20-30% of persons diagnosed with early breast cancer will develop metastatic breast cancer, and in the United States, it is estimated that 155,000 people are currently living with this disease. The most common form of metastatic breast cancer is HR+, HER2 breast cancer, which accounts for approximately 60% of all cases.[3] Metastatic breast cancer is presently incurable. However, current treatments can reduce the spread of cancer to other parts of the body, consequently extending time without disease progression (known as progression-free survival) and enabling patients to live longer—an outcome referred to as "overall survival". Overall survival refers to the days, months, or years that treatment may add to a patient's lifespan. Treatments include blocking the estrogen pathway (hormonal therapy), chemotherapy, and targeted treatments, including treatments that function as CDK 4/6 inhibitors.

CDK4/6 proteins are found in both healthy cells and cancer cells and control how quickly cells grow and divide. In breast cancer, these proteins can become overactive and cause the cells to grow and divide uncontrollably, causing tumor growth. CDK4/6 inhibitors are prescription medications which interrupt these proteins in order to slow or even stop the cancer cells from dividing and causing tumor growth. There are presently three CDK4/6 inhibitors approved by the FDA to treat HR+, HER2 metastatic breast cancer: Verzenio, manufactured by Lilly, Kisqali, made by Novartis and Ibrance, manufactured by Pfizer. All three drugs have been the subject of several significant clinical trials, with overall survival being a key clinical endpoint.

<u>The MONARCH Trials</u>

Lilly's MONARCH-2 study was a published, phase III randomized, double-blinded, placebo-controlled trial which evaluated the efficacy of Verzenio when taken in combination with fulvestrant – a type of hormone therapy which acts as an estrogen receptor that works to block or stop the action of estrogen on cancer cells. The results of MONARCH-2 showed that women taking Verzenio with fulvestrant

[3] "HR" is short for hormone receptor, and most cancer patients are HR+. HER2 is short for human epidermal growth factor receptor 2.

saw a 9.4 month median increase in overall survival compared to women who took fulvestrant alone. Lilly's MONARCH-3 study is an ongoing, yet unpublished, phase III randomized, double-blinded, placebo-controlled trial evaluating the efficacy of Verzenio when taken with a nonsteroidal aromatase inhibitor ("NSAI"). Nonsteroidal aromatase inhibitors are also used alone in the treatment of hormone-dependent breast cancer to inhibit the enzyme aromatase that converts testosterone to estrogen so that the hormone receptors on cancer cells that need estrogen and progesterone to grow cannot proliferate. At an interim overall survival analysis, the results of the MONARCH-3 study showed that Verzenio in combination with an NSAI improved survival outcomes, with a median overall survival of 67.1 months as compared to 54.5 months on an NSAI alone, although these results have not yet reached statistical significance.

The MONALEESA Trials

Novartis' Kisqali treatment has been the subject of three phase III randomized, double-blinded, placebo-controlled clinical trials, each of which achieved statistically significant overall survival outcomes. MONALEESA-7, published in 2019, evaluated the efficacy of Kisqali in combination with endocrine therapy (goserlin and either and NSAI or tamoxifen). Results indicated that median overall survival for patients in the Kisqali group was 58.7 months as compared to an overall survival of 47.7 months for patients receiving endocrine therapy alone. MONALEESA-3, published in 2020, evaluated the efficacy of Kisqali when taken with fulvestrant. Results indicated a median overall survival benefit of 53.7 months for patients taking Kisqali as compared to an overall survival of 41.5 months for women taking fulvestrant alone. Novartis' most recent study, MONALEESA-2, was published in March of this year. MONALEESA-2 studied the efficacy of Kisqali in combination with letrozole. Results demonstrated a median overall survival of 63.9 months for women in the Kisqali group as compared to 51.4 months for women taking letrozole alone.

In June of this year, Novartis issued a press release announcing the results of its latest MONALEESA trial as part of a new advertising campaign directed to both health care professionals and the general public. [4] It is the survival benefit claims made in this campaign that are the subject of the instant challenge. The United States is one of two countries that permits direct to consumer advertising for prescription drugs.

B. The Challenged Advertising

The challenged claims appeared singly or in combination in physician brochures and fliers, conference presentations, a press release and on both the physician and patient directed portions of the Kisqali website. The "longest survival data ever reported in HR+, HER2- mBC." claim also appeared in a minute long commercial which aired on national television. The Challenger argued that Novartis' survival benefit claims went beyond merely reporting the results of its clinical trials and conveyed false and misleading messages about the efficacy of its Kisqali treatment.

[4] Also, in June of this year, Pfizer announced the results of its latest phase III clinical trial. Paloma-2 evaluated the efficacy of Pfizer's Ibrance drug when taken with letrozole. Although patients in the Ibrance group demonstrated a numerically longer overall survival than patients taking letrozole alone, the results were not statistically significant.

C. Permanently Discontinued Claims

During the pendency of the proceedings, the Advertiser informed NAD that it had permanently discontinued the following express and implied claims:

- Live Longer with KISQALI - The Longest Overall Survival Data Ever Reported in HR+, HER2- mBC.
- "The longest survival data ever reported in HR+, HER2- mBC."
- "KISQALI - the longest median overall survival ever reported in HR+/HER2- mBC.
- "Kisqali has the longest median overall survival ever reported in HR+/HER2- metastatic breast cancer."
- Kisqali® provides the longest overall survivability as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio® specifically.
- Patients will live longer with Kisqali as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically.
- Kisqali provides superior survival benefits as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically.

In reliance on the Advertiser's representation that the challenged claims have been permanently discontinued, NAD did not review the claims on their merits. The voluntarily discontinued claims will be treated, for compliance purposes, as though NAD recommended their discontinuance and the Advertiser agreed to comply.

Novartis also informed NAD that the remaining challenged claim "Only drug in class with consistently proven overall survival benefit in HR+/HER2- metastatic breast cancer." would be modified to be accompanied by the phrase "across three phase III trials" or similar language to that effect. NAD therefore reviewed the remaining challenged claim as modified.

D. Analysis

i. The Challenged Claim

On the record provided, the claim "Only drug in class with consistently proven overall survival benefit in HR+/HER2- metastatic breast cancer." * * "across three phase III trials" (the "only drug in class" claim) appears in the headline in a press release and - in a slight variation - as one of several headers in two colored HCP brochures about Kisqali and Novartis' three clinical trials, the latter which are represented both graphically and in text. [5] Specifically, the median overall survival benefit – in years - for each trial is depicted in bold on a vertical bar, and the results of MONALEESA-2 are also displayed in a line graph showing overall survival for Kisqali + AI and overall survival for patients taking the AI + placebo. The details of each study are printed below along with clinical indications for Kisqali and safety and other information about the drug.[6] The Advertiser also indicated to NAD that the "Only

[5] The claim appears on the brochures as "The only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials."

[6] The two page press release, including footnoted references, contains a brief description of MONALEESA-2 and further information about Kisqali performance, recognition and approvals. It also announces that "A matching-adjusted indirect comparison analysis shows that Kisqali plus an aromatase inhibitor (AI) is associated with better symptom - related quality of life when compared to Verzenio plus AI when used in 1L."

drug in class" claim would replace the discontinued "longest survival" claims on the patient facing section of the Kisqali website.

The Challenger argued that the use of the comparative term "only drug in class" renders the claim undeniably comparative and that in context, the claim goes beyond merely reporting Kisqali's efficacy against a placebo in clinical trials and conveys a message of superior survival benefits over other CDK4/6 inhibitors and effectively implies that patients will live longer with Kisqali than when taking any other drug in class – messages which the Challenger contended Novartis has failed to support. First, Lilly argued that the FDA, like NAD, imposes a high bar for claims of comparative clinical effect between products and that Novartis' powerful survival benefit claim must be supported by reliable clinical studies comparing the efficacy of Kisqali to other treatments *and* establishing that patients who take Kisqali will live longer than patients taking Verzenio or any other comparable drug. Lilly pointed out that Novartis had offered no head-to-head clinical study comparing the efficacy of Kisqali to competing CDK4/6 treatments. Further, Lilly argued that achieving statistical significance in certain patient populations does not equate with greater longevity in all HR+, HER2 breast cancer cases.

Secondly, the Challenger argued that given the variability in clinical trial design and the myriad of nuanced differences in the data collected in different trials, comparison of outcomes across clinical studies was fundamentally improper. Lilly pointed out that for example, the comparator arms (endocrine therapy combinations) are not the same in the studies referenced by the Advertiser. The Challenger also noted critical differences between the Lilly and Novartis trials studying Verzenio and Kisqali in combination with fulvestrant, in particular with respect to the clinical profiles of the selected patient populations. Moreover, Lilly argued that even if it was appropriate to compare survival outcomes across trials, Lilly's MONARCH-3 study reported a median overall survival of 67.1 months vs the 63.9 month median overall survival reported in Novartis' MONALEESA-2 study, thus rendering the implied message of Kisqali's superior efficacy patently false.

Finally, Lilly noted that patients with stage IV breast cancer are a particularly vulnerable audience, where a superior survival benefit is not only of utmost importance but also one which is impossible for consumers to be able to evaluate on their own. Lilly also submitted a study indicating that doctors are significantly more likely to prescribe a specific medication when patients ask for it by name and argued that it was critical that Novartis' advertising not overstate the benefits of its Kisqali treatment.

The Advertiser argued that the challenged claim is not a comparative claim but an establishment claim that accurately reports the current state of clinical research in CDK4/6 inhibitors. Secondly, the Advertiser argued that nowhere does Novartis claim superiority over a specific product let alone the entire CDK4/6 market and that the contexts in which the challenged claim appears make clear the limited message it conveys. At best, the Advertiser contended the claim is a parity claim and that Lilly had failed to meet its burden to demonstrate that consumers would take away a superiority message or were otherwise misled by the claim. The Advertiser maintained further that head-to-head testing was not required to support the claim made here, and that in the absence of head-to-head testing (of a significant portion of the market) an advertiser may utilize existing studies on competing products and compare the results against the advertiser's testing to support parity performance claims.

Novartis noted that head-to-head testing was rare in oncological trial design because the focus of clinical trials in this space was to establish the efficacy and benefits of a particular drug and further, that FDA guidance for industry on the design of clinical trials for cancer drugs explicitly envisions a

flexible approach to study designs and outlines the advantages and disadvantages of encouraging a variety of types of clinical support.

Additionally, Novartis emphasized the unique circumstances of the advertising context here and that this was not an ordinary case where advertising is aimed at a lay consumer who individually makes purchases in a supermarket or drugstore. Rather, Kisqali, like other CDK4/6 inhibitors, is prescribed to treat a serious and devastating condition and cannot be obtained without the supervision of a licensed professional. Any patient who is interested in Kisqali must consult with her health care provider, and it is the HCP who will make the ultimate decision about which medication to prescribe. Here, the prescribing physician is almost always an oncologist who will have specialized knowledge and expertise in the treatment of cancer and the sophistication to understand the clinical trial data. As such, any alleged vulnerability of the patient audience will be effectively mitigated by the required consultation with the HCP.

Further, Novartis argued that due to the life-threatening nature of metastatic breast cancer, this particular patient population is more attuned to the science of their condition than patients with less serious illnesses. The Advertiser submitted an article documenting the rise of the "e patient" and the increase in health literacy of cancer patients with the advent of social media and the unprecedented array of resources available to this population on multiples levels, enabling them to play an expanded role in their own care and in larger conversations as to practice, research and policy – in some cases, becoming experts in their own care. The Advertiser contended this sophistication helps inform the net impression target consumers will take away from Novartis' advertising and reinforces the fact that this population is more likely to meaningfully examine the context of advertising for cancer drugs. As such, the use of Kisqali, or any other cancer treatment would be more carefully considered than most other purchasing decisions patient consumers will ever make.

The Advertiser also challenged the probity of the study submitted by the Challenger as to the effects of patient requests on physician prescribing behavior. Novartis noted that the study's authors themselves acknowledged that the presentation of symptoms in an artificial environment may threaten the external validity of the study and that in any event, the real world dynamics of the relationship between the oncologist and cancer patient were much different than the scenarios simulated in the study and that the risks that patient requests could result in an increase in prescriptions for a specific breast cancer drug was not a reasonable let alone plausible concern.

ii. Messages Conveyed

In an NAD proceeding, an advertiser is responsible for all messages reasonably conveyed by the advertising, not merely the message it intended to convey. [7] In the absence of consumer perception evidence, NAD relies on its expertise to determine the messages reasonably conveyed by the challenged advertising.[8] In analyzing the express and implied messages conveyed by a particular advertisement, NAD typically reviews the totality or overall net impression created by an

[7] *i-Health (Culturelle)*, Report # 6196, NAD/CARU Case Reports (June 2018)*; Eddie Bauer, LLC (MicroTherm StormDown Jacket),* Report #5875, NAD/CARU Case Reports (August 2015); *The Proctor & Gamble Company* (*Prilosec*), Report #5261, NAD/CARU Case Reports (December 2010).

[8] *Verizon Communications, Inc. (Verizon 5G Availability,)* Report #6384, NAD/CARU Case Reports (June 2020);*Your Baby Can, LLC (Your Baby Can Read! Early Language Development System)*, Report #5313, NAD/CARU Case Reports (March 2011).

advertisement as a whole, not merely words or phrases standing alone, taking into consideration both the words and the visual images.[9] The degree of sophistication of the target audience is also a factor in determining the reasonable message conveyed by the advertising. [10] Further, NAD has recognized that a claim may be literally true but still misleading.[11]

As a threshold matter, NAD determined that, the claim "Only drug in class with consistently proven overall survival benefit in HR+/HER2- metastatic breast cancer."* * "across three phase III trials" is inherently comparative. By virtue of the phrase "only drug in class", the claim pits Kisqali against all other CDK4/6 inhibitors and posits it has an attribute that the others do not have – here, a consistently proven survival benefit across three clinical trials. [12]

It is also well settled that advertising need not mention a particular competitor specifically in order for the claim to be considered comparative to a rival company.[13] Here, because Lilly is one of Novartis' leading competitors in the manufacture of CDK4/6 treatments, the challenged claim could reasonably

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[9] *Eddie Bauer, LLC (MicroTherm StormDown Jacket*), supra at note 7; *Nurture, Inc. (Happy Family Infant and Toddler Food Products),* Report # 5710, NAD/CARU Case Reports (May2014).

[10] *Mead Johnson & Company (Enfamil NeruoPro Infant Formulas)*, Report #6260, NAD/CARU Case Reports (March 2019); *Bausch & Lomb (PeroxiClear Contact Lens Peroxide Solution)* (ECP's), Report #6025, NAD/CARU Case Reports (November 2016); *Bausch & Lomb, Inc*. (*Advertising for Alcon's OPTI-FREE RepleniSH Solution)* Report #5483, NAD/CARU Case Reports (April 2013); *Nest Labs (Nest Learning Thermostat)* Report # 5595, NAD/CARU Case Reports (May 2013); *Summit VetPharm, LLC (Vectra 3D and Vectra)*, Report #5090, NAD/CARU Case Reports (September 2009), Aff'd NARB Panel#157, (August 2010).

[11] *Chattem, Inc. (Xyzal allergy 24HR),* Report #6146, NAD/CARU Case Reports (January 2018); *ProPhase Labs, Inc. (Cold-EEZE)*, Report #5545, NAD/CARU Case Reports (January 2013); *The Coca-Cola Company (Powerade Sports Drink)*, Report #3930, NAD/CARU Case Reports (July 2002); *Aurora Foods, Inc. (Duncan Hines Chocolate Chip Muffin Mix)*, Report #3623, NAD/CARU Case Reports (February 2000).

[12] NAD also noted that the cases cited by the Advertiser to support its position that Lilly bears the burden of establishing that consumers are taking away a comparative message - a singular departure from established NAD precedent on the parties' respective burdens - are inapposite, as the circumstances prompting NAD to request consumer perception evidence from the challenger in those cases are not present here. *McNeil Consumer Products Company (Motrin IB Pain Reliever),* Report #3535, NAD/CARU Case Reports (April 1999) involved a challenge to the claim "...nothing works better than Motrin IB..." a claim NAD deemed a *"traditional"* parity claim –unlike the clearly comparative claim challenged here. In that early case, NAD acknowledged the body of precedent weighing against the contrary conclusion argued by the challenger and assessed the burden on the challenger to provide evidence that consumers were taking away a superiority message. In *Kraft Foods (Maxwell House Coffee)* Report *#3201,* NAD/CARU Case Reports (June 1995), NAD requested consumer perception evidence from the challenger where the challenger argued that there was *only one* reasonable interpretation of the challenged claim. Moreover, in *Federal Mogul Corp. (ANCO HydroClear Windshield Wipers)*, Report #4420, NAD/CARU Case Reports (August 2004), NAD affirmed that "There is no indication from the language in the Maxwell House decision that NAD's request for a consumer perception study had implications beyond the specific issues in that case, and NAD finds that it does not serve as precedent to require the challenger to submit a consumer perception study in this case. Here, NAD, as always, looked first to the advertiser who, by law, has the burden of establishing a reasonable basis for its claims."

[13] *Church & Dwight Co., Inc. (Arm & Hammer Slide Cat Litter)* Report # 6137, NAD/CARU Case Reports (December 2017); *Progressive Casualty Insurance Co. (Property and Casualty Insurance)*, Report #5577, NAD/CARU Case Reports (April 2013); *Halo Purely for Pets, Inc. (Halo Spot Stew)* Report #5423, NAD/CARU Case Reports (February 2012).

be interpreted as comparative to Lilly's product.[14] NAD next turned to consider the messages conveyed by Novartis' advertising to each of the target audiences.

a. Consumer-Directed Advertising

Clinically proven establishment claims carry great weight with consumers and as such are subject to strict scrutiny. Further, patients suffering from terminal cancer who are looking for options to extend their lived may be especially susceptible to claims about the survival benefit of Kisqali or any cancer treatment advertised to the general public. As discussed earlier, the opening phrase in the claim "Only drug in class with consistently proven survival benefit in HR+/HER2- metastatic breast cancer" * * "across three Phase III trials." sets its object apart from and above the other drugs in its class on the stated metric. Moreover, that metric – survival benefit - is a performance metric, and its unqualified performance message is strengthened by the phrase "consistently proven". Indeed, a reasonable conclusion from the statement that a drug has been consistently - and more often - proven to achieve a statistically significant survival benefit is that that product is more effective. Further, as used here, the term "consistently" implies that the results of trials of competing drugs have been *inconsistent* – a message that, without qualification, is open to negative inferences beyond the mere absence of regularly achieving a statistically significant result. As such, NAD was concerned that to the lay audience, Novartis' quantitative claim could convey a qualitative message.

NAD's decision in *i-Health (Culturelle)*, Report # 6196, NAD/CARU Case Reports (January 2018) is instructive. *i-Health* involved a challenge to a series of clinically proven uniqueness claims about i-Health's Culturelle probiotic supplement. The challenged claims included:

> "LGG is the most clinically proven effective strain*" **Based on the studies of a range of benefits throughout the lifespan.;*
>
> "LGG is the most proven effective strain*" **Based on the number of Lactobacillus rhamnosus GG clinical studies, as of May 2017;*
>
> "Culturelle supports digestive health in overall wellness with the most proven effective probiotic*" **Lactobacillus rhamnosus GG is the most proven effective probiotic strain based on studies for a range of benefits throughout the lifespan.*

[14] Further, in this context, Novartis' press release falls squarely within the definition of "national advertising'" under NAD /NARB Procedures, §1.1: 'The term "national advertising" shall include any paid commercial message, in any medium (including labeling), if it has the purpose of inducing a sale or other commercial transaction or persuading the audience of the value or usefulness of a company, product or service; if it is disseminated nationally or to a substantial portion of the United States, or is test market advertising prepared for national campaigns; and if the content is controlled by the advertiser. See e.g. *Prints Made Easy, Inc. (Online Graphic Design & Customized Printing Services)*, Report #4833, NAD/CARU Case Reports (April 2008); *Brammo Motorsports, LLC (Enertia Electric Motorcycle),* Report # 4828 NAD/CARU Case Reports (April 2008); *Russian Standard Vodka, Inc. (Imperia Vodka)*, Report #4591 NAD/CARU Case Reports (November 2006); See also *Safe Catch, Inc. (Pouched and Canned Tuna),* Report #6911, NAD/CARU Case Reports (July 2021) (making recommendations on challenged claims in advertiser's press release).

NAD determined that the "most proven effective" claims were strong comparative health benefit claims, notwithstanding the absence of a reference to competing products, and that one message reasonably conveyed by the claims was that the strain of probiotic in Culturelle had been proven to be more effective than competing strains in providing the benefits associated with probiotics.[15] Similarly, here Novartis touts that Kisqali is the "only" drug "consistently" proven effective across three clinical trials.

Secondly, NAD was concerned that most consumers do not have the medical knowledge or experience to understand the nuances of clinical trials. They may not appreciate that the results of a clinical trial may be influenced by a variety of factors apart from the quality and efficacy of the tested drug, such as trial design, patient population characteristics, interactions and nature of adjuvant drugs, etc., and as such, they will not understand that outcomes across trials are difficult to compare. Further, the lay consumer will not understand that achieving statistical significance across three clinical trials does not in and of itself establish superior efficacy to other drugs which have proven effective in a smaller number of trials.

The Advertiser argued that cancer patients are a more informed and engaged audience than patients with less serious illnesses and cited an article attesting to the increased healthy literacy of this particular patient population in light of the abundance of resources available on social media, online communities and breast cancer websites. NAD recognized that cancer patients today are empowered with greater knowledge and that they may indeed be more engaged with their plan of care. However, even the totality of resources available to them cannot bridge the knowledge gap between a lay person and an oncologist in the context of understanding the nuances of clinical data and the science behind it.

Novartis also argued that because Kisqali is a prescription drug, it cannot be obtained directly by the patient and that the oncologist can correct any possible misleading messages conveyed by the challenged claim. However, the Advertiser has an obligation to support all messages reasonably conveyed by its advertising. Further, the fact that an oncologist may correct any misinterpretation of Novartis' advertising does not remove the initial impression of the claim, and the initial impression of a claim must not be misleading. [16]

NAD therefore concluded that one message reasonably conveyed to consumers by the "only drug in class" claim is that Kisqali is more effective and provides superior survival benefits to other drugs in its class, including Verzenio, and that patients taking Kisqali will live longer than when taking any other CDK4/6 treatment.

NAD next considered whether the implied message that Kisqali offers superior survival benefits over other drugs in class was supported by the evidence submitted by the Advertiser. It is well settled that

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[15] Further, where the advertiser's evidence showed only that more studies had proven the effectiveness of the LGG strain and not that the advertiser's probiotic had been proven more effective than other probiotics, NAD found that evidence did not provide a reasonable basis for the "most proven effective" claims.

[16] NAD agreed with the Advertiser that due to the artificial nature of the doctor patient encounters in the study submitted by the Challenger, and the very different doctor patient dynamics in the context of treatment of terminal breast cancer, the study was not a reasonable basis to conclude that the challenged claim could lead to increased prescriptions for Kisqali.

health benefit claims must be clear and accurate and supported by competent and reliable scientific evidence,[17] and clinically proven establishment claims are held to a very high standard of proof. [18] It is equally well settled that unqualified superiority claims require testing against all significant competitors in the category.[19] Further, where express or implied comparative performance claims are being made, head-to head studies of the products at issue constitute the most reliable and persuasive substantiation. [20] NAD has also repeatedly recognized in prior decisions that data accumulated from different tests cannot be reliably compared unless it is established that the data resulted from tests that were "essentially identical or all of the variables are accounted for." [21] NAD has thus frequently rejected cross study comparisons where the results of competing studies could not be meaningfully assessed or compared. [22]

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[17] *Mead Johnson (Enfamil NeuroPro Infant Formulas),* supra at note 10; *Wink Naturals, LLC (Zen Drops),* Report #6291 NAD/CARU Case Reports (June 2019); *Prevention Pharmaceuticals, Inc. (Omax3 UltraPure Dietary Supplement)*, Report #5966 NAD/CARU Case Reports (July 2016); *Abbott Nutrition (Similac® Advance® with OptiGRO)*, Report #5859, NAD/CARU Case Reports (June 2015); *Good Health Naturally, LLC (Serranol Supplements)*, Report # 5441 NAD/CARU Case Reports (March 2012).

[18] *OrganiCare (FemiClear Vaginal Yeast Infection Treatment)*, Report #6347 NAD/CARU Case Reports (February 2020); *Bayer Healthcare, LLC (Aleve),* Report # 6310 NAD/CARU Case Reports (September 2019); *Interceuticals, Inc. (Better WOMAN)*, Report # 5485 NAD/CARU Case Reports (July 2012).

[19] *i-Health (Culturelle)*,supra at note 7; *Glaxo Smith Kline, (Super Poligrip)*, Report # 4225 NAD/CARU Case Reports (July 2004); *Discuss Dental (Zoom! Chairside Tooth Whitening System),* Report #4009, NAD/CARU Case Reports (January 2003).

[20] *Johnson & Johnson Consumer, Inc. (Neutrogena UltraSheer Dry-Touch SPF 100+Sunscreen)* Report #6059, NAD/CARU Case Reports (March 2017); *Chattem, Inc. (Xyzal allergy 24HR),* Supra at note 11; *Bayer HealthCare, LLC (Claritin and Claritin-D)* Report #5829 , NAD/CARU Case Reports (April 2015); *Unilever US, Inc.(Vaseline Sheer Infusion)* Report #5262, NAD/CARU Case Reports (December 2010); *Colgate-Palmolive Co. (Colgate Optic White Toothpaste),* Report #5490, NAD/CARU Case Reports (July 2012).

[21] *Colgate-Palmolive Co. (Colgate Optic White Toothpaste), Id.; Discuss Dental (Zoom! Chairside Tooth Whitening System),* supra at note 19; *Procter & Gamble (Crest Whitestrips)*, Report #3918, NAD Case Reports (June 2002); *Den-Mat Corp. (Rembrandt Plus Superior Bleaching System and Dazzling White Tooth Bleaching Value Kit),* Report #3814, NAD Case Reports (September 2001).

[22] *Colgate-Palmolive Co. (Colgate Optic White Toothpaste) Id.*; (disallowing comparison of results of clinical testing on advertiser's toothpaste to results of testing on challenger's product where "studies were conducted at different sites, using different protocols, and using different criteria for participation, with different baselines.) *Unilever US, Inc. (Vaseline Sheer Infusion*), supra at note 20 (rejecting combination of advertiser's monadic sensory testing and statistical PCA (Principal Component Analysis) data to support claim advertiser's product had a "silkier feel" over other lotions); *Novus International, Inc. (Mintrex and MAAC Organic Copper Supplements for Livestock),* Report #5597, NAD/CARU Case Reports (May 2013) (rejecting series of studies on bovine liver copper values to support superiority claim in the absence of statistical analysis of performance of copper supplements as compared to each other and not to placebo); *Procter & Gamble (Crest White Strips)*, supra at note 21 (rejecting cross study comparison because of the "many differences between the [two] studies" submitted.)*; Den-Mat Corp. (Rembrandt Plus Superior Bleaching system and Dazzling White Tooth Bleaching Value Kit), Id.* (disallowing comparison of data from advertiser's product to multiple tests of challenger's Crest Whitestrips where "the methodology varied with respect to the number of people being evaluated, the accompanying dentifrice that was used by test participants and inclusion or omission of pre-test prophylaxis….made a comparison of the resulting data untenable".) *Ecofibers, Inc. (d/b/a Precision Fibers) (Hydroseeding Mulch)* Report #3905, NAD/CARU Case Reports (May 2002) (disallowing comparison of results of two separate studies due to differences in methodologies).

The Advertiser's evidence establishes that in MONALEESA-2, Kisqali had achieved the longest median overall survival outcome in a published clinical trial of CDK4/6 inhibitors. However, Novartis has presented no evidence that the methodologies in the studies it has submitted are similar enough to allow NAD to properly compare the reported overall survival data, nor any statistical analysis of those results. Additionally, Novartis has not provided any details as to the patient populations enrolled in each trial or other critical elements of the trials being compared (such as study design, period of follow-up etc.) Further, as the Challenger pointed out, the evidence in Novartis' literature survey demonstrates that the comparator arms (endocrine therapy combinations) are not the same between the studies it is comparing. There are also important differences even as between the Lilly and Novartis' studies evaluating Verzenio and Kisqali in combination with fulvestrant, especially as to the patient populations enrolled in each trial. For example, MONALEESA-3 enrolled a higher proportion of patients with advanced or metastatic breast cancer who had never received endocrine therapy as treatment for breast cancer (endocrine naïve) while MONARCH-2 excluded these patients from the intent to treat population. Additionally, MONARCH-2 enrolled more patients with clinical features suggestive of endocrine resistant disease.

For the foregoing reasons, NAD determined that the overall survival data from the MONALEESA trials and those of the published studies of competing CDK4/6 treatments did not support the implied superiority messages conveyed by the challenged claim to the lay audience. NAD therefore recommended that in consumer-facing advertising, the Advertiser discontinue the claim "Only drug in class with consistently proven survival benefit in HR+/HER2- metastatic breast cancer" * * "across three Phase III trials" and the following challenged implied claims: 'Kisqali provides superior survival benefits as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically' and 'Patients will live longer with Kisqali as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically.'

b. HCP-Directed Advertising

NAD next considered the "only drug in class" claim in the context of physician- directed advertising. Specifically, NAD considered the claim as it appears in the HCP brochures described earlier: "The only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials." [23] NAD has long recognized that health care providers and specialists are a sophisticated audience and are better equipped to decipher the advertised results of clinical data than the general consumer, especially when provided with appropriate context and detail thereon.[24] NAD has also recognized that the takeaways by discerning professionals may be critically distinct from the interpretations of that same advertising by the lay consumer. For example, in *The Proctor & Gamble Company* (*Prilosec*), Report

[23] Although this iteration of the "only drug in class" claim was not specifically challenged, the claim is substantially similar to the challenged claim as it is proposed to be modified by Novartis. Additionally, NAD deemed it necessary to evaluate this claim in order to determine whether HCP-directed advertising makes the challenged implied claims.

[24] *Mead Johnson (Enfamil NeruoPro Infant Formulas)*, supra at note 10; *Abbot Nutrition* (*Similac Human Milk Fortifier),* Report #5867, NAD/CARU Case Reports (July 2015); *The Procter & Gamble Company (Prilosec OTC)* supra at note 7; *Novartis Consumer Health, Inc. (Transderm Scop Scopolamine Transdermal Patch),* Report # 3717, NAD/CARU Case Reports (January 2001).

#5261, NAD/CARU Case Reports (December 2010), NAD determined that that superior acid claims in P&G's HCP advertising would not be understood more broadly as claims of superior heartburn relief: "In so finding, NAD was again mindful of the fact that the challenged claims are presented to a sophisticated audience of healthcare professionals. Unlike the general consumer, NAD believed that this target audience – with the proper conspicuous disclosure of pertinent information as to the parameters of the [cited] study and the lack of correlation to clinical outcome, was more capable to discern that the comparative claim being made was one of superior acid control and not an implied overall superior heartburn relief claim." Critically, NAD also observed that "In this respect, NAD cautions the advertiser that it is likely, that NAD might have arrived at a different outcome had these claims been directed to the general consumer." [25]

Similarly, NAD determined that the target audience here was more capable of discerning that the comparative claim being made was as to clinical data points and not an implied claim of overall superior efficacy. First, the HCP brochures in which the claim appears contain detailed information about the parameters of all three studies, the latter also reported by a graph similar to the trial representations in Novartis' published studies, extensive drug and safety information and additional notes on toxicities, adverse reactions, lab abnormalities, etc. across all three trials and footnoted references. Secondly, NAD determined that the target audience of oncologists would be well versed in the nuances and intricacies of breast cancer research and fully equipped to appreciate both the significance *and* the limitations of the reported data, especially where, as here, they were provided with sufficient detail as to the trials' design and findings. Unlike consumers, this audience would appreciate what Lilly referred to as the "nuanced differences in data collected from different trials" and that differences in reported outcomes may be the result of factors other than the pure efficacy of the tested drug (such as differences in trial design, methodology and duration, patient population, adjuvant therapies, etc.) For the same reasons, the oncologist/professional audience would understand that although the achievement of a statistically significant survival outcome in more trials than its competitors is a promising result, it is not conclusive that Kisqali provides superior survival benefits or superior survival benefits to all classes of patients with HR+/HER2 metastatic breast cancer.

As such, NAD concluded that clinical experience and the context provided in the brochures would both inform the physician takeaway of the HCP-directed claim and limit it to the recited facts, and that this audience would interpret the comparative claim here simply as reporting that Kisqali is unique in achieving a statistically significant overall survival benefit across Novartis' three phase III clinical trials. For the foregoing reasons, NAD concluded that Novartis' HCP-directed advertising did not convey a message of superior efficacy or the challenged implied claims that 'Kisqali provides superior survival benefits as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically' and that 'Patients will live longer with Kisqali as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically.'

In support of its claim that Kisqali is "The only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials", Novartis presented the results of its three MONALEESA trials

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[25] See also *Mead Johnson (Enfamil Infant formula),* Supra at note 10, where, for the same reasons, NAD advised the advertiser that the video among the challenged advertising items be published by secure portal restricting access to HCP's only.

published in the New England Journal of medicine and the results of a literature search of all reported clinical trials to date of targeted treatments for patients with HR+/HER2 metastatic breast cancer.[26] That evidence established that Kisqali had reached a statistically significant overall survival benefit in all three of its phase III clinical trials. The record also indicates that Lilly's Verzenio has been the subject of three phase III clinical trials: MONARCHplus, MONARCH-2, and MONARCH-3. The results of MONARCHplus were not reported. As described earlier, in MONARCH-2, Verzenio demonstrated a statistically significant overall survival benefit, and MONARCH-3 has reported interim results only that have not yet reached statistical significance.[27] Pfizer's Ibrance treatment, the third of the three FDA approved CDK4/6 inhibitors, has also been studied in three Phase III trials: PALOMA-4, PALOMA-3 and PALOMA-2. The results of PALOMA-4 have not been reported. In PALOMA-3 and in Pfizer's most recent study, PALOMA-2, although patients in the Ibrance group demonstrated a numerically longer overall survival than patients taking the placebo, the results in both trials were not statistically significant.

NAD therefore determined that the Advertiser had provided a reasonable basis for the claim "The only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials." when directed to an HCP audience.

IV. Conclusion

NAD recommended that in consumer-facing advertising, the Advertiser discontinue the express claim "Only drug in class with consistently proven survival benefit in HR+/HER2- metastatic breast cancer."* * "across three phase III trials" and the following challenged implied claims (i) 'Kisqali provides superior survival benefits as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically' and (ii) 'Patients will live longer with Kisqali as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically.'

NAD concluded that Novartis' HCP-directed advertising did not convey a message of superior efficacy nor the challenged implied claims (i) 'Kisqali provides superior survival benefits as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically' and (ii)

[26] The evidence indicated that search terms for the Advertiser's literature review consisted of combinations including: "HR+", "HR-positive", "hormone receptor positive", "HR+/HER2", "metastatic breast cancer", "advanced breast cancer", "survival", and "overall survival". Search engines included PubMed, Google Scholar, and ASCO 2021 Meeting Library. In addition to individual trials returned through the search, a meta-analysis (Lux et al. 2019) and review (Wu et al. 2020) were used as a guide to ensure all appropriate trials that have reported median overall survival were included in the audit. Based on the foregoing, NAD determined that the Advertiser's literature search was a reliable summary of existing clinical studies of survival outcomes in HR+/HER2 metastatic breast cancer.

[27] The parties disputed the import of the interim overall survival benefits reported in MONARCH-3. However, because the weight of the MONARCH-3 results has no bearing on the question of the relative number of trials in which FDA approved CDK4/6 inhibitors have achieved statistical significance, NAD did not reach that issue.

'Patients will live longer with Kisqali as compared to any other available treatment in the CDK 4/6 inhibitor class generally and to Verzenio specifically.'

NAD also concluded that the Advertiser had provided a reasonable basis for the claim "The only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials." when directed to an HCP audience.

V. Advertiser's Statement

Novartis agrees to comply with NAD's recommendation. Novartis is pleased that NAD found that Novartis provided a reasonable basis for its claim that Kisqali is "[t]he only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials," and that this claim does not convey a message of superior efficacy or any of the purported implied claims, when directed to an HCP audience. However, Novartis respectfully disagrees with NAD's findings that the same or substantially similar claim, when directed at consumers, conveys a message "that Kisqali is more effective and provides superior survival benefits to other drugs in its class … and that patients taking Kisqali will live longer than when taking any other CDK4/6 treatment"—messages Novartis does not believe are either expressed or implied by the plain language of the challenged claim. Nevertheless, Novartis will comply with NAD's recommendation and discontinue this claim in its consumer-facing advertising. **(#7137 MCB, closed 12/30/2022)**