The United States Department of Health and Human Services, Food and Drug Administration. November 1, 2022.

Citizen Petition

Date:11-1-2022_

The undersigned submits this petition to Federal Food, Drugs, or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs) to request the Commissioner of Food and Drugs to review and if necessary, revoke an administrative action).

A. Action Requested

Reexamine the results of the DECLARE clinical trial, with particular attention to the use of the combined endpoint of cardiovascular death and hospitalization for heart failure and then answer the questions about this study that are posed at the end of this Petition.

Lem Moyé, M.D., Ph.D. submits this petition to generate action by the Food and Drug Administration involving the indications for the use of dapagliflozin in reducing cardiovascular (CV) death and/or hospitalization for heart failure.

. The basis of this petition is that DECLARE trial that is one of the pivotal studies on which the current approval of dapagliflozin rests violated a methodologic principle in the construction of the combined endpoint of CV death and hospitalization. This has led to a misinterpretation of the data.

The petitioner recognizes important flaws in the interpretation of this data and is thereby asking for the FDA to provide answers to the questions that appear at the end of this petition.

Should the FDA's answers to those questions suggest that the interpretation of the DECLARE trial is invalid because of the improper construction of a combined endpoint, then the petitioner asked that the indication for the use of dapagliflozin to reduce CV death and hospitalization for heart failure be reexamined.

B. Statement of Grounds

The theory of combined endpoints in clinical trials is developed in detail in the "Combined Endpoints Background " section near the end of this petition. Combined or composite endpoints are useful and effective tools to evaluate the effect of therapy in clinical research when the evaluation of the exposure-endpoint relationship is likely to be underpowered because of the low frequency of the endpoint. The F.D.A. has accepted the use of combined endpoints in clinical research. Its use is the state of the art in clinical and public health research. However,

the implementation of these composite endpoints can be complicated. We might be guided in their correct construction and use by the following principles for the use of combined endpoints.

a) Principle 1. Both the combined endpoint and each of its component endpoints must be prospectively specified in detail *(principle of prospective deployment).*

b) Principle 2. The component endpoints under consideration must not be so similar to other components that they add nothing new to the mixture of singleton endpoints that will make up the combined endpoint, yet they should not be so dissimilar that it provides a measure which is customarily not clinically linked to the other component endpoints *(principle of coherence).*

c) Principle 3. The component endpoints that constitute the combined endpoint are commonly given the same weight in the statistical analysis of the research effort. Each of the component endpoints must be measured with the same scrupulous attention to detail. For each component endpoint, it is important to provide documentation not just that the endpoint occurred, but it is equally important to confirm the absence of the component endpoint *(principle of precision).*

d) Principle 4. The analysis of the effect of therapy on the composite endpoint should be accompanied by a tabulation of the effect of the exposure for each of the component endpoints, allowing the reader to determine if there has been any domination of the combined endpoint by any one of its components, or if the findings of the effect of therapy for component endpoints are not consistent *(principle of full disclosure)*.

These principles, particularly Principle 2 are affirmed [1,2], by other authors.

We will see that Principle 2 was violated in the DECLARE clinical trial.

With this as background, we can now review clinical research studies of dapagliflozin. The purpose of this review is to evaluate the risk/benefit balance of dapagliflozin.

Preapproval studies of dapagliflozin. The Endocrinologic and Metabolic Drugs Advisory Committee met on July 19, 2011 to discuss the efficacy and safety of dapagliflozin. The proposed indication of dapagliflozin was as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus (T2DM). The proposed therapeutic dosage is 10 mg for most patients and a 5 mg starting dose for patients at risk for volume depletion due to coexisting conditions or concomitant medications such as loop diuretics.

At the meeting, the cardiovascular safety of dapagliflozin was evaluated through a meta-analysis of 14 randomized clinical trials. The primary endpoint of this meta-analysis was a composite of CV death, myocardial infarction (MI), stroke and hospitalization for unstable angina. The meta-analysis included 78 subjects with 48 of 4287 randomized to dapagliflozin and 30 of 1941 randomized to comparators. The estimated hazard ratio and 98% confidence interval for this endpoint associated with dapagliflozin was 0.67 (0.38, 1.18). The 1.18 upper bound of this confidence interval was smaller than the margin of 1.8 set forth in the FDA Guidance for evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (2008)[1]. This 98% confidence interval was pre-specified (instead of a 95% interval) as part of a two part sequential testing strategy. A statistical review of this meta-analysis was completed by Dr. Anita Abraham on 07 September, 2011.

The vote to approve this drug was split, with many concerns raised about its safety. [3]. Dapagliflozin was found to be associated with increases in bladder cancer. Thus the Advisory Committee meeting expressed serious concerns about the approval of dapagliflozin.

In addition, concerns were raised about the cardiovascular risks associated with the drug. Note, that while in the 2020's the sponsor highlighted cardiovascular "benefit", at the time of the initial drug vote for approval, the concern was not about benefit but hazard attributable to dapagliflozin.

This concern about dapagliflozin causing major cardiovascular concern was based on a meta-analysis of fourteen clinical trials. Major adverse cardiovascular events consisted of cardiovascular death, myocardial infarction, stroke, and hospitalization from arrhythmia. This evaluation revealed no cardiovascular benefit attributable to dapagliflozin, and a possible risk.

In October 2011, Bristol-Myers Squibb and Astra Zeneca submitted an updated meta-analysis of 19 trials to support the cardiovascular safety of dapagliflozin. A statistical review of this meta-analysis was completed by Dr. Anita Abraham on November 22, 2011. The updated 2011 meta-analysis produced an estimated hazard ratio and 95 confidence interval of 0.82 (0.59, 1.38) associated with dapagliflozin relative to all comparators on the risk of the primary pre-specified composite endpoint of: CV death, MI, stroke and hospitalization for unstable angina. In her review, Dr. Abraham concluded that the upper bound of the 95% confidence interval for the risk ratio of CV events "meets the stated 1.8 non-inferiority margin" in accordance with the FDA guidance for cardiovascular safety of products intended to treat type 2 diabetes. The updated 2011 meta-analysis included data up to the first 52 weeks from the then ongoing trials D1690C00018 and D1690C00019. These two trials were conducted in subjects with a history of cardiovascular disease and hypertension. Per request from the FDA, a secondary analysis of cardiovascular safety was conducted in these two trials alone.

However, based on the totality of the data submitted in support of the 2011 application, the FDA denied the approval of dapagliflozin in the United States. In the complete response letter dated 17 January 2011, the FDA expressed concern about the possibility of excess

cardiovascular risk:

"While we cannot conclude that dapagliflozin is associated with an excess CV risk based on an analysis of only these two trials [Studies D1690C00018 and D1690C00019], the findings from these two large, adequate and well-designed trials in a relevant patient population cannot be ignored. More importantly, we cannot include any suggested CV benefit observed in the original meta-analysis in a risk-benefit consideration in regard to the cancer and liver safety signals."[1]

In the same response letter, the FDA provided the following: "To address the above deficiencies, you will need to submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators. At a minimum, the resubmission must include data from patients in studies D1690C00018 and D1690C00019 who have completed at least 52 weeks in these studies."

In response, the sponsors submitted a request for formal dispute resolution to the Office of New Drugs on 17 July 2012. The first item of the request addressed cardiovascular safety. The dispute appeal was denied by the Agency. The response letter stated that:

> The path forward as written in the [complete response letter] is reasonable under the circumstances posed by the data in the NDA and stands as written. This includes the request for updated safety analyses of the NDA database, including at least 52 weeks of data from Studies 18 and 19, but given information that you shared with the review team about event rates at 52 weeks, the full study data, which are expected to be completed with two years of data are imminent and would be far preferable.

This was the motivation for the Sponsors to submit an updated meta-analysis of cardiovascular adverse events conducted in 21 randomized clinical trials for dapagliflozin as part of their application package for NDA 202293.

Meta-analysis and cardiovascular death. The primary meta-analysis population consisted of the randomized, controlled, short term plus long term follow-up periods of the 21 trials. The agreed upon primary composite endpoint to assess CV safety was defined as the time until the first of the following adjudicated events: CV death, heart attacks, stroke, hospitalization for unstable angina. The data follow Tables 3 and 4).

Note that in neither table does dapagliflozin exert a beneficial effect on cardiovascular death. In fact the confidence intervals suggest that there may be an actual hazard with cardiovascular death and this medication. Thus, prior to DECLARE, there was no information suggesting that there was a beneficial effect of this medication on cardiovascular

[1] Statistical Review Application Number 202293Orig1s000 Accessdata fda.gov ndaFDA..

death.

In addition, there is no known mechanism by which dapagliflozin can reduce cardiovascular death. Its effect on cardiovascular hospitalizations for heart failure is certainly concordant with drug's mechanism of action. Dapagliflozin is essentially a diuretic with some serum glucose level lowering ability. As patients lose glucose and some sodium to the urine, water follows into the renal tubules, as an osmotic effect. Therefore, intravascular volume decreases and the workload of the heart decreases, decreasing the magnitude of heart failure if present.

However, this is an effect on heart failure. Cardiovascular death is a different endpoint. It includes death from heart attacks and arrhythmic death (and as we can see, was expanded) There's no mechanism by which this drug affects heart rhythm. Nor does it affect coronary artery thrombotic mechanisms. Inclusion of these components in a combined endpoint violates Principle 2 *vide supra*

Thus, a data-based perspective and a mechanistic perspective together form an argument this medication does not have a beneficial effect on cardiovascular death. With this as background, we now go to the DECLARE clinical trial.

Table 3. Analysis of MACE and the Individual Components of the Primary Composite Outcome in the Population of All 21 Trials

	Comparators	Dapagliflozin		
Events	N = 3403	N = 5936	Estimated HR	Endpoint (95% CI)
MACE	62	73	0.78	(0.55,1.11)
CV Death	18	20	0.71	(0.37,1.37)
MI	33	31	0.59	(0.35,0.97)
Stroke	18	25	1.00	(0.54,1.86)
Hospitalization for unstable angina	20	27	0.91	(0.50,1.66)

Source: Created by reviewer. Dataset: adcv5.xpt

Table 4. Analysis of MACE and the Individual Components of the Primary Composite Outcome in Trials 18 and 19

	Comparators	Dapagliflozin		
Events	N = 945	N = 942	Estimated HR	Endpoint (95% CI)
MACE	29	32	1.11	(0.67,1.83)
CV Death	9	8	0.89	(0.34,2.30)
MI	12	12	1.00	(0.45,2.23)
Stroke	10	12	1.21	(0.52,2.80)
Hospitalization for unstable angina	15	12	0.80	(0.37,1.70)

Source: Created by reviewer. Dataset: adcv5.xpt

Wiviott (2019) [4] conducted the DECLARE clinical trial to assess the cardiovascular risk profile of dapagliflozin.

Design: A randomized double blind clinical trial**.**

Methods: The investigators randomly assigned patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease to receive either dapagliflozin or placebo. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcome was MACE. Secondary efficacy outcomes were a renal composite endpoint of (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause.

However, during the conduct of the trial, a second primary endpoint was added (cardiovascular death or hospitalization for heart failure). Recall that the primary analysis was MACE. The new outcome added several components, (death resulting from an acute myocardial infarction (MI), sudden cardiac death, and death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes) or hospitalization for heart failure. Note that the occurrence of events (MI death, sudden cardiac death, stroke death, procedural death, CV hemorrhagic death) have little to do with the mechanism of action of the drug.

Results: The investigators evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years.

Primary Safety Outcome: In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE (upper boundary of the 95% confidence interval [CI], <1.3; P<0.001 for noninferiority).

Efficacy Analysis 1: Dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17)

Efficacy Analysis 2: Dapagliflozin did result in a lower rate of cardiovascular death or hospitalization for heart failure (the midtrial event that was added) (4.9% vs. 5.8%; hazard ratio, 0.83; 95% CI, 0.73 to 0.95; P=0.005), which reflected a lower rate of hospitalization for heart failure (hazard ratio, 0.73; 95% CI, 0.61 to 0.88); there was no between-group difference in cardiovascular death (hazard ratio, 0.98; 95% CI, 0.82 to 1.17).

Renal: A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (hazard ratio, 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively (hazard ratio, 0.93; 95% CI, 0.82 to 1.04). Diabetic ketoacidosis was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, P=0.02), as was the rate of genital infections that led to discontinuation of the regimen or that were considered to be serious adverse events (0.9% vs. 0.1%, P<0.001).

Authors' Conclusions: In patients with type 2 diabetes mellitus who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure.

Critique: The investigators are skilled clinical trialists; however the interpretation of DECLARE must be carried out with great care.

DECLARE is a study of type 2 diabetes mellitus patients demonstrating that dapagliflozin reduces hospitalization for heart failure. The MACE endpoint of cardiovascular death, heart attack and stroke was an essential choice because it deals directly with the effect of dapagliflozin on major cardiovascular morbidity and mortality (CV death, heart attack, and stroke). It is well accepted by cardiologists and epidemiologists. However, the drug has no known mechanism of action to reduce these events.

Dapagliflozin had no statistically significant effect on this endpoint. It did not reduce major cardiovascular morbidity and mortality. The investigators did a competent job in testing dapagliflozin, but the drug failed the test. This is not uncommon among drugs used in the treatment for the 2 diabetes mellitus.

However the second efficacy endpoint is problematic, CV death/hospitalization for heart failure is problematic. We will consider this endpoint in stages.

First, this endpoint was not prospectively declared but added to DECLARE once the study was underway. This is a hazardous process.[2] The kernel of the inclusion argument must be that no one in trial leadership should have seen the effects of therapy on the new combined endpoint and its components.. This is not convincingly portrayed in the manuscript. Nowhere in the manuscript does it say that each of the component endpoints data incorporated in the combined CV death endpoint was specifically not examined before the new endpoint was certified.

Undermining combined endpoint concordance. This new, midtrial endpoint created by the DECLARE investigators was the first occurrence of either CV death or hospitalization. CV death was defined by the Investigators in the Supplement to the New England Journal of Medicine[3] as

> Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death

[2] In fact, one changes endpoints at great risk because of the danger of generating a random protocol. However the rational of DECLARE's endpoint change was that compelling data from another trial show greater benefit with the new endpoint. This is a change for commercial, not scientific, reasons. Simply put, the DECLARE investigators. wanted the study to be positive, and they changed the endpoint to help ensure that.

[3] Section D: Endpoint and Event Definitions

due to CV hemorrhage, and death due to other CV causes

This endpoint is essentially unrelated to hospitalization for heart failure[4]. This endpoint would become coherent if the death from heart failure was the overwhelming contributor to CV death. But if that were the case, the endpoint contributor would be death from heart failure and not CV death. Therefore we must conclude that death from heart failure was just one contributor to the CV endpoint.[5]

As pointed out in the principles of a combined endpoint *vide supra* the components of a combined endpoint must be related. Specifically they must lie on the same causal pathway, and there should be evidence that the intervention will affect all components. Sudden death, death due to stroke, and death due to CV procedures, for example are not on the same causal pathway as heart failure hospitalization. Nor is there any evidence that CV hemorrhage (another component of CV death) can be impacted by this drug.

An example of a coherent combined endpoint would be a test of aspirin ingestion on fatal and nonfatal heart attacks. Both clinical events lie on the same causal pathway (thrombosis of the coronary arteries) and the manner in which aspirin works suggest that they can both be influenced by this drug.

There is no such concordance with the CV/HF hospitalization endpoint, and it is uninterpretable.

Isolated CV death component: Additionally there was no statistically significant effect of therapy on the CV death component endpoint itself (hazard ratio, 0.98; 95% CI, 0.82 to 1.17). While it is common that combined endpoints judged to have shown a beneficial effect can produce singleton or component endpoint components which are not statistically significant, that conclusion presumes that the combined endpoint is concordant, i.e. the finding of the combined endpoint can be translated to findings for singleton endpoints, which we have seen is not the case in DECLARE.

Others feel the same way, discounting the DECLARE "CV Benefit" e.g., the review of DECLARE by the American College of Cardiology [5] where the authors state the DECLARE demonstrates CV safety but not benefit.

Unfortunately, the Sponsor places misleading ads in the literature discussing the "CV benefit" of dapagliflozin, i.e. proffering that the drug offers a reduction in CV death and hospitalization for heart failure, when there is no CV death reduction.

In fact these ads fly in contravention to the DECLARE investigators, who, in their flagship manuscript state that (page 356),

[4] We will discuss the inclusion of death due to heart failure in the next section.
[5] In fact the absence of disclosure of the distribution of CV deaths is a violation of principle.

> "We did not find that SGLT2 inhibition with dapagliflozin resulted in a lower rate of cardiovascular death or death from any cause than placebo, a finding that contrasts with that in the EMPA-REG OUTCOME trial."

This is refreshing, honest statement from the authors stating, as was seen in the meta-analysis of 21 clinical trials that there is no impact of dapagliflozin on CV death. In addition the FDA did not give approval for an indication in reduction in CV deaths. The combined endpoint findings were dominated by the heart failure endpoint (HR= 0.73 (0.61-0.88), not the CV death endpoint 0.98 (0.82, 1.17).

. The CV death endpoint was considered positive only because the heart failure hospitalization endpoint was positive and CV death was "bundled" into it. Again, that only makes sense if one has a coherent combined endpoint which is not the case in this circumstance.

. Thus, the DECLARE clinical trial does not stand for the hypothesis that CV death reduction is attributable to dapagliflozin. Any ad stating the contrary is misrepresenting this drug.

The invalidation of the hospitalization endpoint in DECLARE. The second component of this new efficacy endpoint in DECLARE is hospitalization for heart failure. While this is a critical endpoint component to have in a heart failure study, it cannot stand by itself.

This is because the heart failure hospitalization endpoint only includes the morbid, nonfatal component of the disease, excluding the fatal component. Analyzing only hospitalization for heart failure is a classic and lethal mistake in the field. It is quite possible that the drug can both reduce hospitalizations for heart failure, but also increase the overall heart failure death rate. This would happen, for example, if patients exposed to the therapy experienced accelerated heart failure that led to death at home or work before they could be hospitalized. In this case, the study would report lower hospitalization rates, missing the increased death rate from heart failure. Such events would be missed if one has an endpoint that only includes hospitalization for heart failure.

The natural epidemiologic solution for this problem is to add a fatal heart failure endpoint component. The natural choice would be death from heart failure. This inclusion would close off the escape of events that were important in tabulating heart failure events, but did not lead to hospitalization.

. It is clear that the investigators had this information about fatal heart failure events; as was pointed out earlier, it was included in the definition for CV death. Why it was not extracted and combined to form a coherent combined endpoint of fatal/nonfatal heart failure (or even broken out and reported separately), is an important question that goes unanswered.

Therefore the evaluation of hospitalization for heart failure in and of itself is epidemiologically incomplete, unresponsive, and would not support the conclusion that the medication reduces heart failure. DECLARE stands for neither a reduction in CV death, nor in heart failure hospitalizations. In the end it reduces HbA1c.

Combined Endpoints Background

Combined endpoints: The combined endpoint is of interest in studies involving the study of the effect of oral hypoglycemic agents on the clinical manifestations of diabetes mellitus. They play a central role in DECLARE.

They are commonly invoked when the use of a single endpoint would produce a sample size that is exorbitant. In this circumstance there are two useful solutions to this dilemma. One is to increase the size of the study. The best designed studies are those that are designed to have small type I errors and high power, a set of conditions, which produces larger, rather than smaller sample sizes. However, sometimes it would be impractical to increase the sample size substantially. In that case, another approach is to increase the frequency of the endpoint in which one is interested. The required sample size to detect an effect is related to the frequency of the endpoint one is interested in detecting.

The more frequent the endpoint occurs (i.e., the greater its frequency in the population), the smaller the sample needs to be to produce them. Therefore, an approach that is accepted in research methodology is to create a combined endpoint [1].

A combined endpoint includes not just one but instead a collection of several endpoints each of which could stand as an endpoint in a study. An example would be the combination of ventricular septal defects, neural tube defects and polydactyly. We will call each part of this endpoint a component or singleton endpoint. In this case each of these three singleton endpoints could serve as its own standalone endpoint in a study. However, the combination of these endpoints permits a larger event rate, and therefore a smaller sample size. For example, an event that occurs in 1 per thousand per year requires 47,182 patients two detect an odds ratio of 2.0 with a type I error of 0.05 and 80% power. However, if this is combined with a second event whose rate is also one per thousand per year, the combined endpoint event rate is $1-0.999^2=0.002$ and a sample size of 23,630. The combination of five such events, each occurring at a rate of 0.001 produces a combined endpoint event rate of $1-0.999^5=0.004$ and a sample size of 11,854. Thus the more components contained in a combined endpoint, the more frequent the number of endpoints, and the smaller the sample size required to detect the effect of the therapy.

However, an important, and predictable corollary of this combined endpoint approach is that since smaller samples are required, one is less likely to see each of the singleton endpoints in the smaller sample. We anticipated this because infrequent singleton endpoints require larger sample sizes than does the combined endpoint. The smaller sample size is designed to identify at least one singleton endpoints of the combined endpoint, not each of them individually. Thus, the absence of singleton endpoints in the sample does not mean there is no relationship between the exposure and the endpoint, especially if there is a relationship between the exposure and the combined

endpoint. This is a critical conclusion, which we must hold to when we interpret studies using the combined endpoint. There do not have to be examples of the particular singleton endpoint in the study for the combined endpoint findings to apply to them. However, to be convincing the combined endpoint must be carefully constructed.

Mathematics of Combined Endpoints: We can explore some of the aforementioned concepts about combined endpoints mathematically. Assume that we have two component endpoints A and B. The incidence rate of component A (per unit time) we express as a probability, or P [A]. If this were the only endpoint of the study, the sample size would be based on P [A] and as we have seen, the smaller P [A], the larger the study must be. However, suppose we identify a second endpoint B, with its own incidence rate, P [B]. The combined endpoint would be the combination of these two; specifically it would be the occurrence of either A or B or both. This expresses at the union of $\boldsymbol{A}$ and $\boldsymbol{B}$, or $A \cup B$ We may think of this as the occurrence of at least one of A and B, i.e., A occurs, B occurs, or they both occur. The occurrence of both is expressed as $A \cap B$. The correct expression for the occurrence of the combined endpoint is

$$\mathbf{P}[A \cup B] = \mathbf{P}[A] + \mathbf{P}[B] - \mathbf{P}[A \cap B]$$

This union is what the combined endpoint measures. We may think of it as measuring the occurrence of at least one of singleton endpoints A and B. Note that we cannot just sum the incidence rates because the two endpoint A and B may occur together. This is an important observation about the component endpoints of combined endpoints. They themselves may be related, i.e., they may occasionally (but not always expected to) occur in the same individual at the same time. The incidence of this occurrence is expressed as $\mathbf{P}[A \cap B]$. The need to subtract is evident from the following Venn diagram

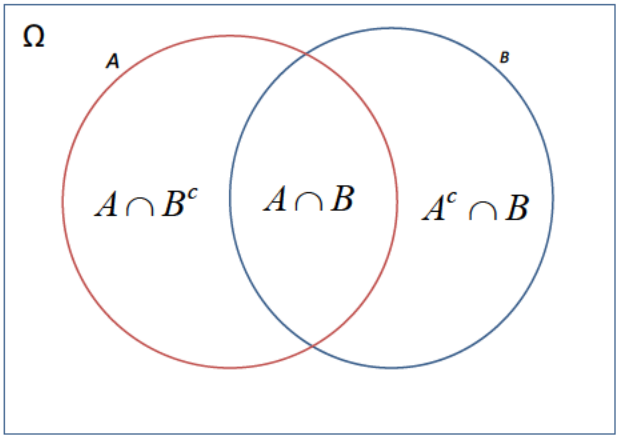

Figure 1.

(A^c in Figure 1 simply means "not A"). Clearly just adding $\mathbf{P}[A]$ and $\mathbf{P}[B]$ **adds** $\mathbf{P}[A \cap B]$ twice; one of them must be removed. Hence the expression $\mathbf{P}[A \cup B] = \mathbf{P}[A] + \mathbf{P}[B] - \mathbf{P}[A \cap B]$.

However there are circumstances where the event A and B are not seen together. We call such events disjoint events, and write $\mathbf{P}[A \cap B] = 0$. Component endpoints that are disjoint may seem to offer an advantage since $\mathbf{P}[A \cup B] = \mathbf{P}[A] + \mathbf{P}[B]$ is at a maximum and provides the smallest sample size. However, it may not make sense to combine singleton endpoints that are themselves disjoint. Events that are disjoint do not measure pathophysiology in common, and it is what they have in common that drives the rationality of the combination. For example, they may have in common the same underlying disease e.g., stroke and heart attack in patients with diabetes mellitus. While clearly strokes are not heart attacks, they have a common root connection to diabetes i.e., the change in the blood vessels supplying both the heart and the brain that are directly linked to the disease.

An example of the use of a combined endpoint is the CARE study [6]. The investigators examined the role of cholesterol reduction therapy in 4,159 patients. Patients were randomized and followed for five years. The combined endpoint was fatal heart attack or nonfatal heart attack, i.e., a patient was considered a "case" if either they had died of a heart attack, or they survived but had an attack. The *p*- value for the combined endpoint in this randomized study was 0.003 with a risk reduction of 24% (95% CI 9% to 36%). However, if we look at one of the components of the combined endpoint, examining the evidence for benefit, we see that, for example, for the fatal component of this endpoint (fatal heart attack), the *p*-value is 0.10 and the risk reduction is 20% (95% CI –5 to 39). Is it reasonable to conclude that the drug does not reduce fatal heart attacks? Certainly not. It's much more likely that the investigators were simply unable to infer a difference in the fatal event rate in the population, based on the very small number of fatal heart attacks in the sample. But since the combined endpoint was intelligently chosen and cholesterol is linked to both fatal and nonfatal heart attacks, then the effect of the medication is to reduce the incidence of each singleton endpoint.

Coincident Endpoints: Another consideration in the construction of a combined endpoints is the occurrence of coincident singleton endpoints. Coincident endpoints are endpoints whose pattern is such that the occurrence of one is wholly or almost wholly subsumed by the other. In this case coincident singleton endpoints *A* and *B* are such that singleton endpoint *A* is wholly contained in singleton endpoint *B* and therefore $\mathbf{P}[A \cap B] = \mathbf{P}[A]$. Little is gained in combining then into a single combined endpoints since here

$$\mathbf{P}[A \cup B] = \mathbf{P}[A] + \mathbf{P}[B] - \mathbf{P}[A \cap B] \approx \mathbf{P}[A] + \mathbf{P}[B] - \mathbf{P}[A] = \mathbf{P}[B].$$

Thus, the ideal composite endpoint is one where the singleton endpoints are related to each other (i.e., they are not disjoint) nor are they coincident. With this as background we can examine the role of combined endpoints in studying exposure risk in congenital heart disease and other major malformations.

Using Combined Endpoints: Combined endpoints are useful and effective tools to evaluate the effect of therapy in clinical research when the evaluation of the exposure-endpoint relationship is likely to be underpowered because of the low frequency of the

endpoint. The F.D.A. has accepted the use of combined endpoints in clinical research. Its use is the state of the art in clinical and public health research. However, we have seen the implementation of these composite endpoints can be complicated. We might be guided by the following principles for the use of combined endpoints, from [**Error! Bookmark not defined.**]

Principle 1. Both the combined endpoint and each of its component endpoints must be prospectively specified in detail *(principle of prospective deployment).*

Principle 2.The component endpoints under consideration must not be so similar to other components that they add nothing new to the mixture of singleton endpoints that will make up the combined endpoint, yet they should not be so dissimilar that it provides a measure which is customarily not clinically linked to the other component endpoints *(principle of coherence).*

Principle 3. The component endpoints that constitute the combined endpoint are commonly given the same weight in the statistical analysis of the research effort. Each of the component endpoints must be measured with the same scrupulous attention to detail. For each component endpoint, it is important to provide documentation not just that the endpoint occurred, but it is equally important to confirm the absence of the component endpoint *(principle of precision).*

Principle 4. The analysis of the effect of therapy on the composite endpoint should be accompanied by a tabulation of the effect of the exposure for each of the component endpoints, allowing the reader to determine if there has been any domination of the combined endpoint by any one of its components, or if the findings of the effect of therapy for component endpoints are not consistent *(principle of full disclosure)*.

Thus, wielded affectedly composite endpoints are a very useful tool. They permit the sensitive detections of harm signals in relatively small and efficient sample sizes, and following the tools of good research design elaborated earlier (e.g., prospective design and selection of endpoints, and adequate sample size for those endpoints) can permit observations that are generalizable to the population at large.

With this as background, The petitioner would like the FDA to answer the following questions.

1. What specifically was the role of the October 2011 Sponsor updated meta-analysis of 19 trials in the decision to ultimately approve dapagliflozin for effectiveness in reducing CV death or hospitalization from heart failure.

   Regarding the DECLARE trial published by Wiviott. et.al in the New England Journal of Medicine.

2. Were the FDA reviewers aware that the original endpoint of the DECLARE was MACE comprised of cardiovascular death, myocardial infarction, or ischemic stroke?

3. Were the FDA reviewers aware that this endpoint was changed during the. conduct of the study?

4. Were the FDA reviewers satisfied that neither the trial leadership, nor investigators, nor sponsor looked at each of the CV death combined endpoint components before they made the decision to include this with hospitalization for heart failure as a new efficacy endpoint] (This was not specifically stated in the manuscript)?

5. Where the FDA reviewers aware that the cardiovascular death endpoint ultimately included MI death? Sudden cardiac death? Stroke death? Procedural death? Hemorrhagic death?

Assuming that combined endpoint must have component endpoints that 1) are along the same causal pathway and 2) be affected by dapagliflozin:

6. What is the mechanistic evidence that dapagliflozin influences the acute MI death rate?

7. What is the evidence that hospitalization for heart failure is related to AMI?

8. What is the specific mechanistic evidence suggesting dapagliflozin affects sudden cardiac death?

9. What is the evidence that hospitalization for heart failure is related to sudden death?

10. What is the mechanism suggesting that dapagliflozin affects stroke deaths?

11. What is the evidence that hospitalization for heart failure is related to stroke deaths?

12. Where is the specific mechanistic evidence that dapagliflozin influences the rate of procedural deaths?

13. What is the evidence that hospitalization for heart failure is related to procedural deaths?

14. Where is the evidence demonstrating the mechanism by which dapagliflozin affects the rate of hemorrhagic death?

15. What is the evidence that hospitalization for heart failure is related to hemorrhagic deaths?

16. What is the evidence suggesting that the mechanism of action of dapagliflozin affects "death due to other causes"?

17. What is the evidence that hospitalization for heart failure is related to death due to other causes"?

18. What is the evidence suggesting that the mechanism of action of dapagliflozin affects procedural deaths.

19. What is the evidence that hospitalization for heart failure is related to procedural deaths.

20. Given that a combined endpoint, in order. to be persuasive, must include component endpoints that are both 1) on the same causal pathway, and 2) are likely to be influenced by therapy, do the answers to questions six to nineteen above support the use of the CV death/hospitalization for heart failure as a combined endpoint for DECLARE?

21. Given the possibility that a drug may decrease the event rate of a morbid endpoint, (hospitalization for heart failure) but increase the event rate for the mortal endpoint (heart failure death), is there justification for hospitalization for heart failure being a stand-alone endpoint?

22. If the answers to questions twenty and twenty-one are in the negative, then does DECLARE clinical trial serve as a basis for the approval of dapagliflozin for the reduction of CV death.

C Environmental impact statement.
The petitioners believe the actions requested in this petition provides us no significant environmental impact. The requested action will not introduce any substance into the environment as categorically excluded. Pursuing 21 CFR 25. 30.

D Economic impact statement.
The information is only to be submitted when requested by the Commissioner following the review of this petition.

E Certification.
The undersigned certifies that the best knowledge and belief of the undersigned this petition includes all information and views on which the petitioner relies, and that includes representative data and information known to the petitioner, which are unfavorable to the position.

(b) (6)

Lem Moyé, M.D., Ph.D.
(b) (6) [redacted]

References

1 McCoy CE. Understanding the Use of Composite Endpoints in Clinical Trials. *West J Emerg Med*. 2018;19(4):631-634. doi:10.5811/westjem.2018.4.38383

2. Lia M. Palileo-Villanueva, Antonio L. Dans,Composite endpoints,Journal of Clinical Epidemiology,Volume 128,2020,Pages 157-158,ISSN 0895-4356,

3 Transcript of the endocrinologic and metabolic drugs advisory committee meeting on Tuesday, July 19th, 2011.

4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357. doi: 10.1056/NEJMoa1812389. Epub 2018 Nov 10. PMID: 30415602.

5 https://www.acc.org/latest-in-cardiology/clinical-trials/2018/11/08/23/09/declare-timi-58 (last accesses April 26, 2022)

6. Sacks FM, Pfeffer MA, Moyé, LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335(14):1001-9.