CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND #	130647
Request Receipt Date	August 10, 2020
Product	FARXIGA (dapagliflozin) 10 mg Oral Tablets
Indication	Delay the progression of CKD and prevent hospitalization for heart failure and death in adults with chronic kidney disease
Drug Class/Mechanism of Action	Sodium-glucose co-transporter 2 (SGLT2) inhibitor
Sponsor	AstraZeneca
ODE/Division	OCHEN/Division of Cardiology and Nephrology
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	October 9, 2020

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Delay the progression of CKD and prevent hospitalization for heart failure and death in adults with chronic kidney disease

2. **Are the data supporting the BTDR from trials/IND(s) that are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) and to reduce the risk of hospitalization for

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

heart failure in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. It is also approved for the treatment of heart failure (in patients with and without T2DM) to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). The submitted request for breakthrough therapy designation perstains to the use of dapagliflozin to delay the progression of chronic kidney disease (CKD) and prevent hospitalization for heart failure and cardiovascular or renal death in patients with CKD.

The term CKD encompasses a heterogenous collection of diseases, and no product is approved to delay progression of kidney disease in the proposed broad population, although there are interventions (such as blood pressure control) that are thought to slow progression across the various etiologies of disease. There are also approved therapies for some etiologies of CKD. The angiotensin converting enzyme inhibitor (ACE inhibitor) captopril is approved for the treatment of diabetic nephropathy in patients with type 1 diabetes mellitus (T1DM). The angiotensin receptor blockers (ARBs) irbesartan and losartan and the SGLT2 inhibitor canagliflozin are approved for the treatment of diabetic nephropathy in patients with T2DM. ACE inhibitors and ARBs are commonly used regardless of the etiology of kidney disease. Tolvaptan is approved for the treatment of autosomal dominant polycystic kidney disease (ADPKD).

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The sponsor cites analyses of the primary endpoint (a composite of 50% decline in eGFR, ESRD, and cardiovascular [CV] or renal death) and secondary endpoints (a composite of a 50% decline in eGFR, ESRD, and renal death; a composite of CV death and hospitalization for heart failure; and all-cause mortality) from the DAPA-CKD trial.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

The primary endpoint for DAPA-CKD is similar to those used historically to support the traditional approval of therapies intended to treat common chronic kidney diseases.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

For slowly-progressive, uncommon kidney diseases, the Division has accepted treatment effects on the rate of loss of kidney function (e.g., eGFR slope) as a basis for traditional approval. For primary glomerular diseases that manifest with substantial proteinuria, the Division has also accepted complete remission or near “normalization” of proteinuria in patients with substantial baseline proteinuria as a basis for full approval and lesser, but still substantial effects as a basis for accelerated approval. To date, the Division has not widely accepted such surrogate endpoints as a basis for traditional approval for common kidney diseases, although there has been recent interest from sponsors to explore situations where this may be an acceptable approach, and the Divison has expressed willingness to pursue such discussions..

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

As noted above, there are no therapies approved to delay the progression of kidney disease in a broad population of patients. Current treatments include management of the underlying cause of CKD, when possible, and comorbidities that can hasten CKD progression such as hypertension. ACE inhibitors and ARBs, approved for patients with T1DM and T2DM, respectively, are also commonly used regardless of the underlying etiology of CKD.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

No other applications in the Division have requested the designation for such a broad indication.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The DAPA-CKD trial was a randomized, double-blind, placebo-controlled trial to evaluate the effect of once daily dapagliflozin 10 mg vs. placebo in 4304 patients with CKD, an eGFR ≥ 25 and ≤ 75 mL/min/1.73m^2, and albuminuria ≥ 200 and ≤ 5000 mg/g with T2DM (n=2906) or without T2DM (n=1398).

As shown in Table 1, the trial was successful on its primary endpoint, a composite of ≥ 50% sustained eGFR decline, ESRD (sustained eGFR < 15 mL/min/1.73 m^2, chronic dialysis, renal transplant), and CV or renal death (HR 0.61 [95% CI 0.51 to 0.72], p<0.0001). All components contributed to the observed effect.

Table 1: Primary Endpoint Results

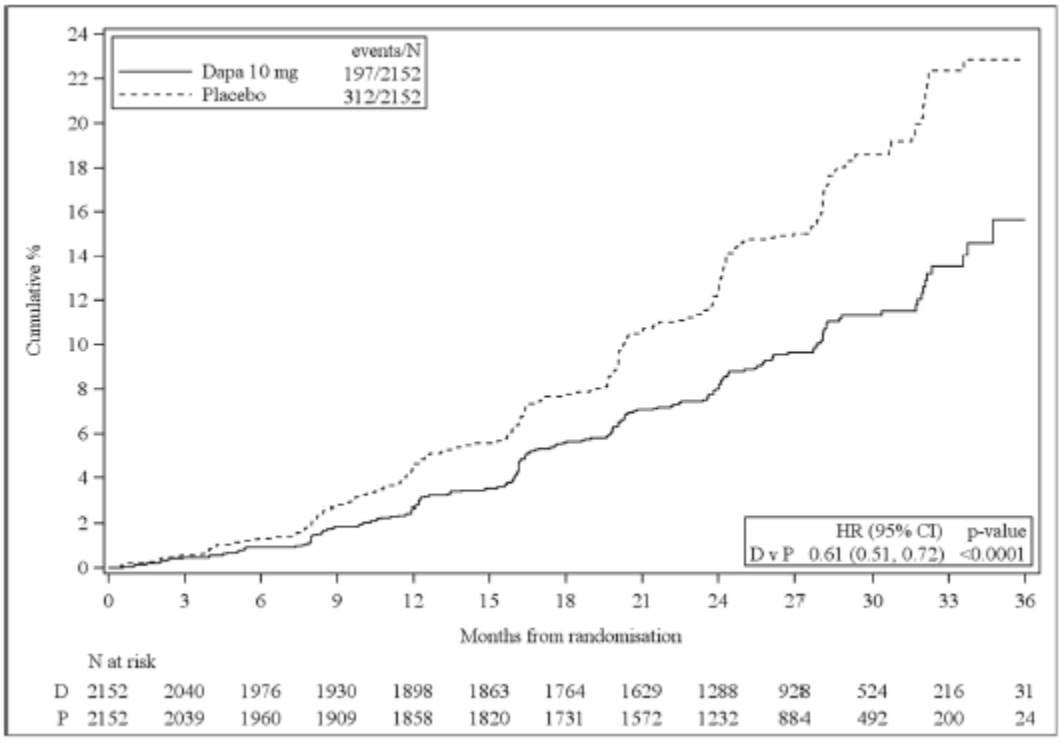
	Dapa 10 mg (N=2152)		Placebo (N=2152)				
Variable	**Subjects with events n (%)**	**Event rate**	**Subjects with events n (%)**	**Event rate**	**HR**	**95% CI**	**p-value**
Composite of ≥ 50% eGFR decline, ESRD, and renal or CV death	197 (9.2)	4.6	312 (14.5)	7.5	0.61	(0.51, 0.72)	<0.0001
≥ 50% decline in eGFR	112 (5.2)	2.6	201 (9.3)	4.8	0.53	(0.42, 0.67)	<0.0001
ESRD	109 (5.1)	2.5	161 (7.5)	3.8	0.64	(0.50, 0.82)	0.0004
eGFR < 15mL/min/1.73 m^2	84 (3.9)	1.9	120 (5.6)	2.8	0.67	(0.51, 0.88)	0.0045
Chronic dialysis[a]	68 (3.2)	1.5	99 (4.6)	2.2	0.66	(0.48, 0.90)	0.0080
Receiving renal transplant[a]	3 (0.1)	0.1	8 (0.4)	0.2			
Renal death[a]	2 (<0.1)	0.0	6 (0.3)	0.1			
CV death[a]	65 (3.0)	1.4	80 (3.7)	1.7	0.81	(0.58, 1.12)	0.2029

Source: Sponsor, Request for Breakthrough Therapy Designation, Table 3.

The Kaplan-Meier curves separated early and continued to separate throughout the trial (Figure 1).

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Figure 1: Kaplan-Meier of Primary Endpoint



Source: Sponsor, Request for Breakthrough Therapy Designation, Figure 1.

The trial was also successful on its secondary endpoints, a renal secondary endpoint (primary endpoint without CV death; HR 0.56 [95% CI 0.45 to 0.68], $p < 0.0001$), a composite of CV death and hospitalization for heart failure (Table 2; HR 0.71 [95% CI 0.55 to 0.92], $p = 0.0089$), and all-cause mortality (HR 0.69 [95% CI 0.53 to 0.88], $p = 0.0035$).

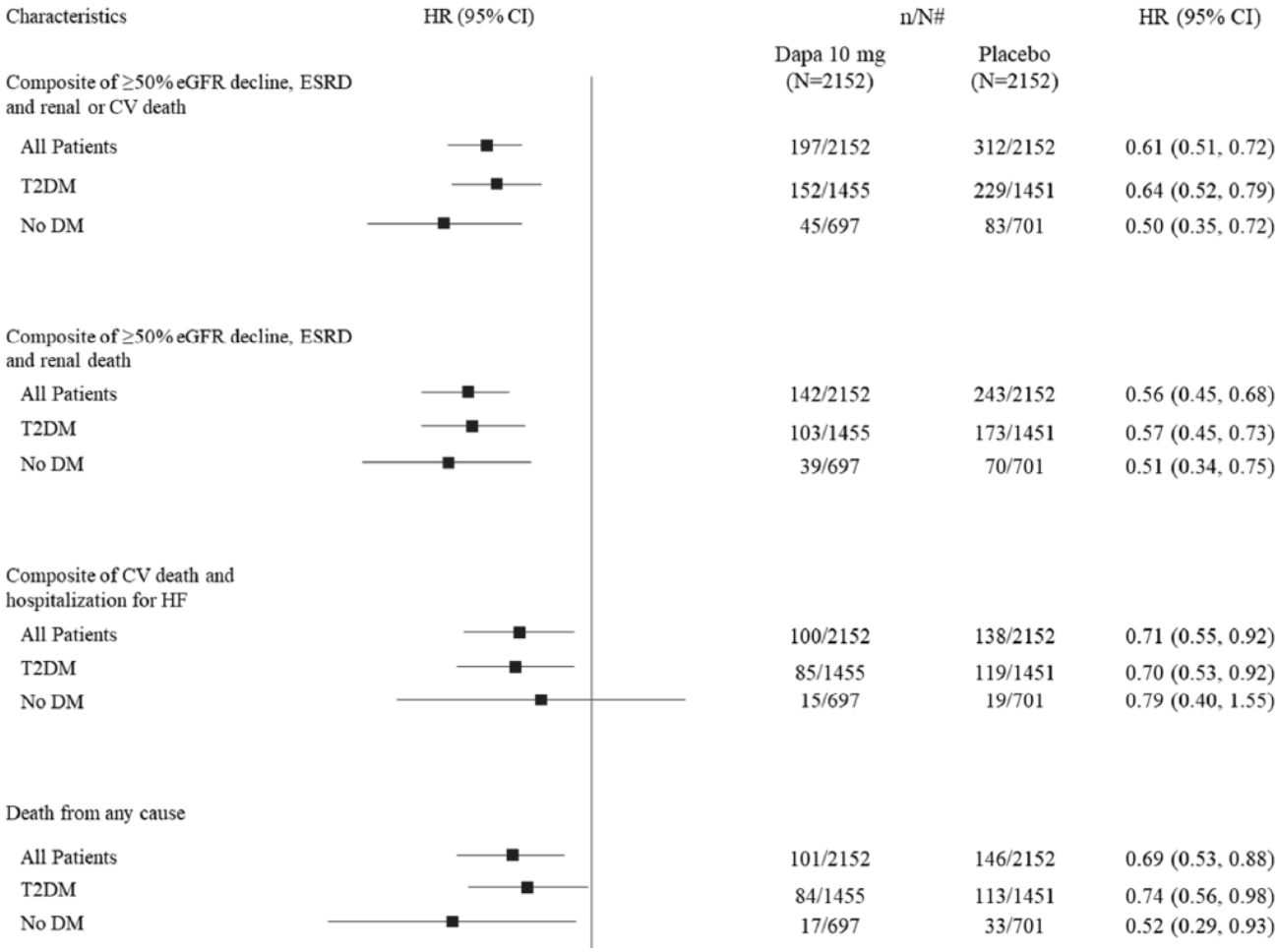
Table 2: Secondary Endpoint: Cardiovascular Death and Hospitalization for Heart Failure

	Dapa 10 mg (N=2152)		Placebo (N=2152)				
Variable	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	HR	95% CI	p-value
Composite of CV death and hospitalization for HF	100 (4.6)	2.2	138 (6.4)	3.0	0.71	(0.55, 0.92)	0.0089
Hospitalization for HF	37 (1.7)	0.8	71 (3.3)	1.6	0.51	(0.34, 0.76)	0.0007
CV death	65 (3.0)	1.4	80 (3.7)	1.7	0.81	(0.58, 1.12)	0.2029

Source: Sponsor, Request for Breakthrough Therapy Designation, Table 4.

Of note, the results of the primary and secondary endpoints were consistent in patients with and without T2DM (Figure 2).

Figure 2: Subgroup Analysis by Diabetes Status



Source: Sponsor, Request for Breakthrough Therapy Designation, Table 3.

b. Include any additional relevant information.

There are several marketed SGLT2 inhibitors and the risk profile is well-established.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: The DAPA-CKD trial provides promising clinical evidence that dapagliflozin demonstrates a substantial improvement over available therapies on clinically significant endpoints, including, notably, in patients with CKD without diabetes. Canagliflozin, another SGLT2 inhibitor class, is indicated for the treatment of diabetic nephropathy in patients with T2DM. Although the breadth of the indication will be a review issue, dapagliflozin would be the first agent indicated for a broader population of patients with CKD without diabetes, a population with significant unmet need.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The sponsor is currently preparing an efficacy supplement based on the results of the DAPA-CKD trial, (b) (4), (b) (5)

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Team Leader Signature: {See appended electronic signature page}
Deputy Director Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 3/18/19/M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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