CLAIMS

1. Use of dapagliflozin in the manufacture of a pharmaceutical composition for reducing the rate of cardiovascular death and worsening heart failure in a patient with heart failure with reduced ejection fraction (HFrEF), wherein the pharmaceutical composition comprising a therapeutically effective amount of dapagliflozin is to be administered to the patient;

wherein the patient does not have type II diabetes;

wherein the pharmaceutical composition is to be administered to the patient with at least one standard of care HF agent; and

wherein the rate for cardiovascular death and worsening heart failure is reduced relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

2. The use of claim 1, wherein worsening heart failure comprises unplanned hospitalization(s) for heart failure and/or urgent heart failure visit(s).

3. The use of claim 2, wherein unplanned hospitalization(s) for heart failure is due to one or more of the following:

(a) new or worsening symptoms of HF experienced by the patient, and/or

(b) objective evidence of new or worsening symptoms of HF; and/or

(c) initiation of intensification of treatment specifically for HF.

4. The use of claim 3, wherein unplanned hospitalization(s) for heart failure includes first and/or recurrent hospitalizations for HF.

5. The use of claim 2, wherein urgent HF visit(s) includes one or more of the following:

(a) an emergency room visit for a primary diagnosis of HF, not requiring hospitalization;

(b) an emergency room visit for a primary diagnosis of HF, requiring treatment other than just an increase in oral diuretics, but not requiring hospitalization;

(c) an urgent unscheduled visit to a physician’s office for a primary diagnosis of HF;

(d) an urgent unscheduled visit to a physician’s office requiring treatment other than just an increase in oral diuretics;

(e) initiation or intensification of treatment specifically for HF; and/or

(f) initiation of intravenous therapy.

6. The use of claim 1, wherein the amount of dapagliflozin to be administered is 10 mg daily.

7. The use of claim 1, wherein the use further improves heart failure symptoms.

8. The use of claim 7, wherein the improvement in heart failure symptoms is measured by a patient's higher score on the KCCQ TSS compared to the patient's score prior to initiation of the use of the pharmaceutical composition comprising the therapeutically effective amount of dapagliflozin.

9. The use of claim 8, wherein the higher score on the KCCQ TSS is at least 5 points higher than the score prior to the use of the pharmaceutical composition comprising the therapeutically effective amount of dapagliflozin.

10. The use of claim 8, wherein the higher score on the KCCQ TSS is at least 10 points higher than the score prior to the use of the pharmaceutical composition comprising the therapeutically effective amount of dapagliflozin.

11. The use of claim 8, wherein the higher score on the KCCQ TSS is at least 15 points higher than the score prior to the use of the pharmaceutical composition comprising the therapeutically effective amount of dapagliflozin.

12. The use of claim 7, wherein the improvement in heart failure symptoms is measured by a patient's lower deterioration in score on the KCCQ TSS relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

13. The use of claim 1, wherein the use satisfies at least one of the following conditions:

(a) the use results in a hazard ratio for time to first composite endpoint of hospitalization for HF, cardiovascular death or urgent HF visit that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(b) the use results in a hazard ratio for time to first composite endpoint of hospitalization for HF, cardiovascular death or urgent HF visit that is statistically nominally less

than one in a patient relative to an administration regimen where the patient receives at least one standard care HF agent alone;

(c) the use results in a hazard ratio for time to first composite endpoint of hospitalization for HF, cardiovascular death or urgent HF visit at eighteen (18) months of approximately 0.73 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(d) the use results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of hospitalization for HF, cardiovascular death or urgent HF visit at eighteen (18) months of 0.60 to 0.88 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(e) the use numerically reduces that absolute risk of the composite endpoint of hospitalization for HF, cardiovascular death or urgent HF visit in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(f) the use results in a nominally significant risk reduction of the composite endpoint of hospitalization for HF, cardiovascular death or urgent HF visit in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(g) the use results in a numerical reduction in the composite endpoint events of hospitalization for HF, cardiovascular death or urgent HF visit in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(h) the use results in a numerical reduction in the rate of composite endpoint events of hospitalization for HF, cardiovascular death or urgent HF visit in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(i) the use results in a hazard ratio for time to cardiovascular death that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(j) the use results in a hazard ratio for time to cardiovascular death that is nominally significantly less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(k) the use results in a hazard ratio for time to cardiovascular death at eighteen (18) months of approximately 0.85 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(l) the use results in a 95% confidence interval for the hazard ratio for time to cardiovascular death at eighteen (18) months of 0.66 to 1.10 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(m) the use results in a hazard ratio for time to first composite endpoint of hospitalization for HF or urgent HF visit that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(n) the use results in a hazard ratio for time to first composite endpoint of hospitalization for HF or urgent HF visit that is statistically nominally less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(o) the use results in a hazard ratio for time to first composite endpoint of hospitalization for HF or urgent HF visit at eighteen (18) months of approximately 0.62 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(p) the use results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of hospitalization for HF or urgent HF visit at eighteen (18) months of 0.48 to 0.80 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(q) the use results in a hazard ratio for time to first hospitalization for HF that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(r) the use results in a hazard ratio for time to first hospitalization for HF that is statistically nominally less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(s) the use results in a hazard ratio for time to first hospitalization for HF at eighteen (18) months of approximately 0.63 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(t) the use results in a 95% confidence interval for the hazard ratio for time to first hospitalization for HF at eighteen (18) months of 0.48 to 0.81 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(u) the use results in a decrease in mean change of NT-proBNP levels in a patient within 8 months of the start of treatment, relative to an administration regimen where the patient receives at least one standard of care HF agent alone; and/or

(v) the use results in a decrease in mean change of NT-probBNP levels of -278 pg/ml in a patient within 8 months of the start of treatment, relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

14. The use of claim 1, wherein the use satisfies at least one of the following conditions:

(a) the use results in a hazard ratio for time to composite endpoint of hospitalization for HF or cardiovascular death that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(b) the use results in a hazard ratio for time to composite endpoint of hospitalization for HF or cardiovascular death that is statistically nominally less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(c) the use results in a hazard ratio for time to composite endpoint of hospitalization for HF or cardiovascular death at eighteen (18) months of approximately 0.73 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(d) the use results in a 95% confidence interval for the hazard ratio for time to composite endpoint of hospitalization for HF or cardiovascular death at eighteen (18) months of 0.60 to 0.89 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(e) the use numerically reduces the absolute risk of the composite endpoint of hospitalization for HF or cardiovascular death in a patient relative to an administration regimen where the patient receives at least standard of care HF agent alone;

(f) the use results in a nominally significant reduction in the rate of the composite endpoint of hospitalization for HF or cardiovascular death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(g) the use results in a numerical reduction in the composite endpoint of hospitalization for HF or cardiovascular death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone; and/or

(h) the use results in a numerical reduction in the rate of composite endpoint of hospitalization for HF or cardiovascular death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

15. The use of claim 1, wherein the use satisfies at least one of the following conditions:

(a) the use results in a hazard ratio for time to all-cause mortality that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(b) the use results in a hazard ratio for time to all-cause mortality that is nominally significantly less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(c) the use results in a hazard ratio for time to all-cause mortality at eighteen (18) months of approximately 0.88 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(d) the use results in a 95% confidence interval for the hazard ratio for time to all-cause mortality at eighteen (18) months of 0.70 to 1.12 in a patient relative to an administrative regimen where the patient receives at least one standard of care HF agent alone;

(e) the use numerically reduces the absolute risk of all-cause mortality relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(f) the use results in a nominally significant reduction in the rate of all-cause mortality in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(g) the use results in a numerical reduction in all-cause mortality relative to an administration regimen where the patient receives at least one standard of care HF agent alone; and/or

(h) the use results in a numerical reduction in the rate of all-cause mortality in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

16. The use of claim 1, wherein the use satisfies at least one of the following conditions:

(a) the use results in a rate ratio for total number of hospitalizations for HF events (first and recurrent) and CV death that is less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(b) the use results in a rate ratio for total number of hospitalizations for HF events (first and recurrent) and CV death that is nominally significantly less than one in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(c) the use results in a rate ratio for total number of hospitalizations for HF events (first and recurrent) and CV death at eighteen (18) months of approximately 0.73 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(d) the use results in a 95% confidence interval for the rate ratio for total number of hospitalizations for HF events (first and recurrent) and CV death at eighteen (18) months of 0.59 to 0.91 in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(e) the use numerically reduces the absolute risk of the total number of hospitalizations for HF events (first and recurrent) and CV death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(f) the use results in a nominally significant reduction in the rate of total number of hospitalizations for HF events (first and recurrent) and CV death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone;

(g) the use results in a numerical reduction in the total number of hospitalizations for HF events (first and recurrent) and CV death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone; and/or

(h) the use results in a numerical reduction in the rate of total number of hospitalizations for HF events (first and recurrent) and CV death in a patient relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

17. Use of dapagliflozin in the manufacture of a pharmaceutical composition for reducing the rate of hospitalization for heart failure and cardiovascular death in a patient following an acute myocardial infarction, wherein the pharmaceutical composition comprising a therapeutically effective amount of dapagliflozin is to be administered to the patient;

wherein the patient does not have type II diabetes;

wherein the pharmaceutical composition is to be administered to the patient with at least one standard of care HF agent; and

wherein the rate for hospitalization for heart failure and cardiovascular death is reduced relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

18. The use of claim 17, wherein the patient has experienced an acute myocardial infarction within 7 days from initiation of the use of the pharmaceutical composition comprising the therapeutically effective amount of dapagliflozin.

19. The use of claim 18, where the acute myocardial infarction is a ST segment elevation myocardial infarction (STEMI) or a non-ST segment elevation myocardial infarction.

20. The use of claim 17, wherein the hospitalizations for heart failure is due to one or more of the following:

(i) new or worsening symptoms of HF experienced by the patient;

(ii) objective evidence of new or worsening symptoms of HF; and/or

(iii) initiation or intensification of treatment specifically for HF.

21. The use of claim 17, wherein the hospitalizations for heart failure includes first and/or recurrent hospitalizations for HF.

22. Use of dapagliflozin in the manufacture of a pharmaceutical composition for reducing the rate of cardiovascular death or worsening heart failure symptoms in patients with acute decompensated heart failure, wherein the pharmaceutical composition comprising a therapeutically effective amount of dapagliflozin is to be administered to the patient;

wherein the patient does not have type II diabetes;

wherein the pharmaceutical composition is to be administered to the patient with at least one standard of care HF agent; and

wherein the rate for cardiovascular death and worsening heart failure is reduced relative to an administration regimen where the patient receives at least one standard of care HF agent alone.

23. The use of claim 22, wherein the patient is hospitalized in stable condition for worsening heart failure symptoms or acute decompensated heart failure.

24. The use of claim 22, wherein the patient has a left ventricular ejection fraction (LVEF) of less than or equal to 40%.

25. The use of claim 22, wherein the reduction in the rate of worsening heart failure symptoms is satisfied by a reduction in hospitalizations for heart failure or reduction in urgent HF visits.

26. The use of claim 25, wherein the hospitalizations for heart failure includes first and/or recurrent hospitalizations for HF and is due to one or more of the following:

(i) new or worsening symptoms of HF experienced by the patient;

(ii) objective evidence of new or worsening symptoms of HF; and/or

(iii) initiation or intensification of treatment specifically for HF.

27. The use of claim 25, wherein the urgent HF visits requires treatment for worsening heart failure other than just an increase in oral diuretics.

28. Use of SGLT2 inhibitor in the manufacture of a pharmaceutical composition for reducing the risk of hyperkalemia in patients with heart failure, wherein the pharmaceutical composition comprising a therapeutically effective amount of SGLT2 inhibitor is to be administered to the patient.

29. The use of claim 28, wherein the risk of hyperkalemia is associated with MRA use in a patient with heart failure.

30. The use of claim 28, wherein a therapeutically effective amount of AZD9977 or a pharmaceutically acceptable salt thereof is to be further administered to the patient.