Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eText

Study population for analysis of effectiveness and safety

The pre-specified Statistical Analysis Plan defined the selection of subjects to be included in the analyses in the following manner (Section 7.2 of the Statistical Analysis Plan):

Selection of Subjects to be included in the Analyses

Intent-to-treat (ITT)

- Received at least one dose of Triple Combination Pill for the Intervention arm
- Some post-randomization data of SBP and DBP are available

Safety

- Some post-randomization data relating to safety are available.

The following statement provides clarification of the definitions used:

Intent-to-treat (ITT)

- All patients randomized to Triple Combination Pill received at least one dose of Triple Combination Pill. The ITT population therefore included all randomized participants.
- Patients with missing BP data for any particular visit were not included for efficacy analyses for that visit (missing data for SBP and DBP were not imputed for any visit, as fewer than 10% of data were missing - Section 6.2 of the Statistical Analysis Plan)
- For every efficacy variable, the analysis included all randomized patient with data available for that variable.

Safety

- All except 7 randomized patients had some post-randomization data recorded. It cannot be confirmed whether or not there was any opportunity to report adverse events in these 7 patients.

To maximize comparability in the assessment of efficacy and safety, the ITT population (i.e. all randomized patients) has been used for all analyses in the study report, including all available data. However due to the ambiguity in the definition of the Safety population, we have repeated the adverse event analyses excluding the 7 randomized patients without any post-randomization data recorded. The findings are presented in eTable 6 and do not alter the conclusions.

Product manufacture and quality control for over-encapsulated Triple Combination Pill

Study capsules were manufactured by Pharmaceutical Packaging Professionals, Melbourne, Australia, a current Good Manufacturing Practice certified company. Individual component tablets, all approved by the Australian Therapeutic Goods Administration, were over-encapsulated with gelatin capsules.

The first batch of approximately 6,700 capsules was hand filled, which involved opening the capsules and placing one of each tablet into the capsule. The remaining capsules were filled using a semi-automatic process with a capsule filler that holds and splits 300 capsules.

As capsules were not sealed, all returned capsules were precision weighed at the end of the study as a quality control exercise. For returned capsules in bottles the capsule error rates (representing potential over-filling or under-filling of capsules) for manually filled and semi-automated batches were 0.40% and 0.33%, respectively, of total capsules. For samples retained by the manufacturer the overall error rate was 0.04%. This suggests that a small number of study participants and/or center staff may have opened capsules, contributing to the higher error rate in returned capsules.

Methods for blood pressure measurement

Instructions provided in Manual of Procedures

1. Participants should be asked to avoid smoking or drinking tea/coffee, exercise for at least 30 minutes before measuring the blood pressure (BP).
2. Allow the participants to sit for at least 5 minutes in a quiet room before beginning BP measurement.
3. Arm circumference (AC) should be measured midway between the shoulder tip and the olecranon process. If AC <32cm use standard cuff (12-13cm long and 35m wide); if AC ≥32cm use large cuff. If arm circumference <24cm use the standard cuff adjusting the cuff as appropriate.
4. Have the cuff at the heart level, whatever the position of the patient.
5. Measure heart rate by pulse palpation and check for atrial fibrillation. In the circumstance of atrial fibrillation, revert to using a standard mechanical sphygmomanometer.
6. Take three measurements spaced by 1–2 minutes, and additional measurements if the second and third readings differ by more than 10mmHg SBP or 5mmHg DBP. Ensure that the BP reading is printed after each measurement, and attached to the BP measurement log. The eCRF will calculate the average of the 2nd and 3rd readings automatically.
7. Record the average of the second and third readings for average systolic and diastolic BP.
8. Ensure blood pressure is measured using the same arm and same cuff size at subsequent visits throughout the trial.

Wait 1-2 minutes before repeating the BP measurement (steps 9. to 12.) in the same arm.

Definitions of adverse event and serious adverse event

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event:

Any untoward medical occurrence during a clinical trial that is associated with any of the following:

- Death
- Life-threatening condition
- In-patient hospitalization
- Prolongation of hospitalization
- Persistent or significant disability or incapacity
- A congenital anomaly or birth defect

eTable 1. Listing of standard daily doses of blood pressure medication used in the study

Medication	**Standard daily dose**
Amiloride	10 mg
Amlodipine	5 mg
Atenolol	50 mg
Bisoprolol	10 mg
Captopril	100 mg
Carvedilol	25 mg
Chlorthalidone	25 mg
Diltiazem	180 mg
Enalapril	20 mg
Furosemide	40 mg
Hydrochlorothiazide	25 mg
Indapamide	2.5 mg
Losartan	50 mg
Metoprolol	100 mg
Nebivolol	5 mg
Nifedipine	40 mg
Perindopril arginine	5 mg
Prazosin	2 mg
Propanolol	160 mg
Ramipril	2.5 mg
Spironolactone	50 mg
Telmisartan	40 mg
Verapamil	240 mg

Based on as described by Bennett et al[21] and Law et al.[14]

eTable 2. Baseline characteristics by randomized group and blood pressure lowering drug use at baseline

	Triple Combination Pill (N=349)		**Usual Care (N=351)**	
Characteristics	**Not on treatment N=209**	**Monotherapy N=140**	**Not on treatment N=204**	**Monotherapy N=147**
Age (years)	54.2 (11.8)	59.8 (9.6)	54.9 (10.9)	57.5 (10.3)
Female sex – no. (%)	109 (52.2%)	98 (70.0%)	105 (52.0%)	91 (62.0%)
Anti-platelet use – no. (%)				
Aspirin	10 (4.8%)	26 (18.6%)	6 (3.0%)	22 (15.0%)
Clopidogrel	3 (1.4%)	7 (5.0%)	2 (1.0%)	8 (5.4%)
Statin use – no. (%)	25 (12.0%)	72 (51.4%)	10 (4.9%)	74 (50.3%)
Current tobacco use (Cigarette, cigar or chewing – no. (%)	24 (11.5%)	15 (10.7%)	22 (10.8%)	12 (8.2%)
Current alcohol use – no (%)	28 (13.4%)	14 (10%)	22 (10.8%)	12 (8.2%)
Medical history – no. (%)				
History of coronary artery disease	13 (6.2%)	17 (12.1)	8 (3.9%)	14 (9.5%)
History of cerebrovascular disease	2 (1.0%)	11 (7.9%)	2 (1.0%)	5 (3.4%)
Chronic kidney disease	1 (0.5%)	6 (4.3%)	1 (0.5%)	2 (1.4%)
Type 1 Diabetes	0 (0.0%)	1 (0.7%)	0 (0%)	1 (0.7%)

	Triple Combination Pill (N=349)		Usual Care (N=351)	
Characteristics	**Not on treatment N=209**	**Monotherapy N=140**	**Not on treatment N=204**	**Monotherapy N=147**
Type 2 Diabetes	40 (19.1%)	71 (50.7%)	43 (21.1%)	64 (43.5%)
Gout	0 (0.0%)	1 (0.7%)	1 (0.5%)	1 (0.7%)
Physiological variables				
Systolic blood pressure – mmHg (mean ± SD)	155.4 (10.7)	152.4 (12.0)	155.7 (11.0)	152.0 (12.1)
<130	1 (0.5%)	3 (2.1%)	0 (0.0%)	2 (1.4%)
≥130 to <140	11 (5.3%)	19 (13.6%)	12 (5.9%)	22 (15.0%)
≥140 to <150	61 (29.2%)	38 (27.1%)	57 (27.9%)	48 (32.7%)
≥ 150	136 (65.1%)	80 (57.1%)	135 (66.2%)	75 (51.0%)
Diastolic blood pressure – mmHg (mean ± SD)	91.9 (8.7)	85.8 (9.9)	91.9 (9.1)	87.3 (9.9)
< 80	17 (8.1%)	40 (28.6%)	23 (11.3%)	36 (24.5%)
≥80 to <90	56 (26.8%)	50 (35.7%)	51 (25.0%)	47 (32.0%)
≥90 to <100	98 (46.9%)	39 (27.9%)	88 (43.1%)	56 (38.1%)
≥ 100	38 (18.2%)	11 (7.9%)	42 (20.6%)	8 (5.4%)
eGFR - mL/min/1.73m2 (mean ± SD)	92.3 (19.3)	86.8 (19.8)	93.2 (18.2)	89.9 (19.0)
<30 mL/min/1.73m2	3/209 (1.4%)	1/204 (0.5%)	1/140 (0.7%)	2/147 (1.4%)
≥ 30 to <50 mL/min/1.73m2	3/209 (1.4%)	3/204 (1.5%)	9/140 (6.4%)	1/147 (0.7%)
≥50 mL/min/1.73m2	203/209 (97.1%)	200/204 (98.0%)	130/140 (92.9%)	144/147 (98.0%)

	Triple Combination Pill (N=349)		Usual Care (N=351)	
Characteristics	**Not on treatment N=209**	**Monotherapy N=140**	**Not on treatment N=204**	**Monotherapy N=147**
Heart rate – beats per minute (mean ± SD)	78.5 (12.1)	77.6 (13.0)	77.9 (11.6)	77.9 (11.4)
Overweight (BMI ≥ 25 to 30 kg/m^2) – no. (%)	74 (35.4)	67 (32.8)	42 (30.0%)	54 (36.7%)
Obese (BMI > 30 kg/m^2)	37 (17.7)	27 (19.3)	37 (18.1)	31 (21.1)
LDL cholesterol – mg/dL (mean ± SD)	132.4 (41.0)	111.1 (39.0)	135.6 (41.1)	115.7 (38.9)
HDL cholesterol – mg/dL (mean ± SD)	46.8 (12.9)	48.7 (12.1)	46.3 (12.4)	45.6 (12.8)
Triglycerides – mg/dL (mean ± SD)	162.0 (84.8)	142.5 (79.6)	169.1 (86.5)	152.4 (76.5)
Glucose (combined fasting and non-fasting) – mg/dL (mean ± SD)	111.5 (42.9)	127.7 (66.2)	115.5 (49.1)	127.6 (62.3)
Type 1 Diabetes[a]	N/A	120.00 (N/A)	N/A	123.00 (N/A)
Type 2 Diabetes	160.0 (56.7)	157.2 (81.4)	170.4 (70.4)	163.6 (75.4)
No Diabetes	100.0 (28.9)	97.0 (16.9)	100.8 (27.0)	99.6 (27.8)
Creatinine - mg/dL (mean ± SD)	0.90 (1.0)	0.86 (0.6)	0.82 (0.3)	0.82 (0.3)
Urine albumin:creatinine ratio – mg/g (median, IQR)	17.0 (8.0, 40.0)	17.0 (10.0, 40.0)	18.0 (9.0, 52.0)	17.0 (9.0, 42.0)

[a]In the 'Not on treatment' group there were no patients with Type 1 Diabetes and only two patients in the Monotherapy group – one in each randomized group.

eTable 3. Sensitivity analysis for primary and secondary BP targets outcomes using Fully Conditional Specification for multiple imputation

Visit	Relative risk (95% CI)	P value
Achieving BP target		
Week 6	1.51 (1.31; 1.74)	<.0001
Week 12	1.50 (1.32; 1.71)	<.0001
Week 24	1.23 (1.09; 1.39)	0.0006
Mean change in BP	**Modeled treatment effect (95% CI)**	
Mean (SEM) change in SBP at 6 months – mm Hg	-8.7 (-11.0; -6.3)	<.0001
Mean (SEM) change in DBP at 6 months – mm Hg	-4.5 (-6.0; -3.1)	<.0001

eTable 4. Reasons for discontinuing any blood pressure lowering medication by group

	Triple Combination Pill (N=349)	**Usual Care (N=351)**
Dizziness	6 (1.7%)	2 (0.6%)
Cough	0 (0.0%)	6 (1.7%)
Hypotension	3 (0.9%)	5 (1.4%)
Headache	1 (0.3%)	1 (0.3%)
Edema	2 (0.6%)	3 (0.9%)
Nausea or Vomiting	1 (0.3%)	0 (0.0%)
Constipation	0 (0.0%)	1 (0.3%)
Electrolyte imbalance	3 (0.9%)	4 (1.1%)
Ankle/pedal oedema	0 (0.0%)	3 (0.9%)
Mild chest pain	1 (0.3%)	1 (0.3%)
Loss of appetite	1 (0.3%)	0 (0.0%)
Difficult breathing	1 (0.3%)	0 (0.0%)
Headache/gastritis/dizziness[a]	1 (0.3%)	0 (0.0%)
Hypersensitivity	1 (0.3%)	0 (0.0%)
Dyspepsia	1 (0.0%)	0 (0.0%)
Unspecified adverse event	1 (0.3%)	1 (0.3%)
Increased urinary albumin creatinine ratio	0 (0.0%)	1 (0.3%)

[a]all three reported as one event.

eTable 5. Number of blood pressure lowering classes and number of blood pressure lowering pills taken by randomized group, and by baseline therapy

	Baseline		6 weeks		12 weeks		6 months	
	Triple Combination Pill	**Usual Care**	**Triple Combination pill**	**Usual Care**	**Triple Combination Pill**	**Usual Care**	**Triple Combination Pill**	**Usual Care**
Not on treatment at baseline								
Data available	209	204	203	201	201	199	200	196
Mean number of BP lowering classes	0.0	0.0	2.9	1.2	2.9	1.3	2.8	1.4
Mean number of BP lowering pills	0.0	0.0	1.1	2.0	1.1	2.2	1.1	2.3
Monotherapy at baseline								
Data Available	140	147	136	146	136	146	134	145
Mean number of BP lowering classes	1.0	1.0	2.8	1.2	2.8	1.3	2.7	1.4
Mean number of BP lowering pills	1.8	1.8	1.1	2.1	1.2	2.4	1.2	2.4

eTable 6. Adverse events, serious adverse events and changes in laboratory parameters in the safety population as defined in the statistical analysis plan

	Triple Combination Pill (N=344)	**Usual Care (N=349)**
Participants with at least one adverse event, no. (%)	133 (38.7%)	121 (34.7%)
Participants with at least one serious adverse event, no. (%)	27 (7.8%)	21 (6.0%)
Participants discontinuing a blood pressure lowering medication due to an adverse event, no. (%)	23 (6.7%)	24 (6.9%)
Laboratory parameters –Mean change (SEM) levels from baseline to 6 months;		
LDL cholesterol – mg/dL	-4.8 (2.9)	-12.9 (2.8)
HDL cholesterol – mg/dL	1.0 (0.6)	1.1 (0.6)
Triglycerides – mg/dL	-27.2 (4.9)	-26.9 (4.8)
Creatinine – mg/dL	0.07 (0.04)	0.03 (0.04)
Uric acid – mg/dL	0.6 (0.07)	-0.04 (0.07)
Sodium – mmol/L	-0.03 (0.16)	0.67 (0.16)
Potassium – mmol/L	-0.11 (0.04)	0.11 (0.03)
ALT – IU/L	-1.5 (1.1)	-3.8 (1.1)
AST – IU/L	-1.5 (0.9)	-1.9 (0.8)
Glucose – mg/dL	0.5 (3.2)	-1.8 (3.1)
UACR – mg/g	-40.8 (5.7)	-21.9 (5.7)

CI denotes confidence interval. SEM denotes standard error of mean.

To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for blood glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, ALT alanine transaminase, AST aspartate transaminase, UACR urinary albumin creatinine ratio.

eTable 7. Classification of reported serious adverse events

	Triple Combination Pill (N=349)	**Usual Care (N=351)**
Total number of participants with at least one serious adverse event	27 (7.7%)	21 (6.0%)
Death	0 (0.0%)	2 (0.6%)
Life threatening	1 (0.3%)	0 (0.0%)
In-patient Hospitalization	26 (7.4%)	19 (5.4%)
Prolongation of hospitalization	0 (0.0%)	0 (0.0%)
Persistent/Significant Disability/Incapacity	0 (0.0%)	0 (0.0%)
Congenital Anomaly or Birth Defect	0 (0.0%)	0 (0.0%)

eTable 8. Change in urinary albumin-creatinine ratio from baseline to 6 months by subgroups defined by baseline characteristics

Subgroup	n	Triple Pill (N=349) Mean change (95% CI)	Usual Care (N=351) Mean change (95% CI)	Mean difference[a] (95% CI)	P-value	P-value Heterogeneity
Age						
< 57 years	318	-40.6 (-56.5, -24.6)	-33.3 (-49.1, -17.5)	-7.3 (-29.7, 15.1)	0.52	0.15
≥ 57 years	322	-41.6 (-57.6, -25.7)	-11.3 (-26.9, 4.4)	-30.4 (-52.6, -8.1)	0.01	
Sex						
Male	268	-35.5 (-53.1, -17.9)	-0.7 (-17.4, 16.1)	-34.8 (-59.1, -10.6)	0.01	0.08
Female	372	-45.0 (-59.5, -30.5)	-38.7 (-53.4, -24.0)	-6.3 (-26.9, 14.3)	0.55	
Diabetes						
No	445	-39.6 (-53.1, -26.1)	-29.0 (-42.5, -15.5)	-10.6 (-29.5, 8.4)	0.27	0.12
Yes	195	-44.7 (-65.7, -23.7)	-6.9 (-27.3, 13.6)	-37.8 (-66.5, -9.2)	0.01	
Median eGFR						
< 94.3 mL/min/1.73m2	313	-33.3 (-49.2, -17.3)	-7.1 (-23.0, 8.9)	-26.2 (-48.7, -3.7)	0.02	0.40
≥ 94.3 mL/min/1.73m2	327	-48.8 (-64.6, -33.1)	-36.2 (-51.6, -20.8)	-12.6 (-34.6, 9.4)	0.26	
SBP						

Subgroup	n	Triple Pill (N=349) Mean change (95% CI)	Usual Care (N=351) Mean change (95% CI)	Mean difference[a] (95% CI)	P-value	P-value Heterogeneity
< 148 mmHg	210	-44.7 (-64.7, -24.6)	-15.8 (-35.0, 3.4)	-28.9 (-56.6, -1.2)	0.04	0.69
148 - 159.5 mmHg	226	-35.1 (-53.5, -16.6)	-22.4 (-41.7, -3.1)	-12.7 (-39.3, 14.0)	0.35	
> 159.5 mmHg	204	-44.7 (-64.9, -24.6)	-28.6 (-48.3, -9.0)	-16.1 (-44.2, 12.0)	0.26	
DBP						
< 85.5 mmHg	207	-35.1 (-55.0, -15.1)	-14.6 (-34.4, 5.1)	-20.4 (-48.3, 7.4)	0.15	0.73
85.5 - 94.5 mmHg	222	-43.5 (-61.7, -25.4)	-16.6 (-36.6, 3.4)	-26.9 (-54.0, 0.2)	0.05	
> 94.5 mmHg	211	-44.6 (-65.6, -23.5)	-33.4 (-51.8, -14.9)	-11.2 (-39.0, 16.6)	0.43	
Blood pressure prescription						
No	380	-31.9 (-48.1, -15.8)	-9.1 (-25.9, 7.7)	-22.9 (-43.4, -2.4)	0.03	0.64
Yes	260	-56.2 (-77.9, -34.6)	-401.0 (-62.1, -19.9)	-15.3 (-40.0, 9.5)	0.23	

[a] Mean difference for continuous outcomes estimated from an analysis of covariance. CI denotes confidence interval. eGFR denotes estimated glomerular filtration rate. SBP denotes systolic blood pressure. DBP denotes diastolic blood pressure.

eTable 9. Fasting LDL cholesterol, triglycerides and glucose at the final (6 month) study visit

Parameter		Triple Combination Pill	Usual Care	Mean Difference[a]	P-value
HDL cholesterol (mg/dL)	n	293	294	587	
	Mean (SEM)	48.5 (0.9)	47.7 (0.9)	0.8 (-1.3, 2.9)	0.46
LDL cholesterol (mg/dL)	n	293	294	587	
	Mean (SEM)	118.9 (3.1)	112.3 (3.1)	6.6 (-0.01, 13.2)	0.05
Triglycerides (mg/dL)	n	292	294	586	
	Mean (SEM)	122.0 (3.3)	126.1 (3.3)	-4.2 (-13.3, 5.0)	0.37
Glucose (mg/dL)	n	293	294	587	
	Mean (SEM)	115.8 (3.2)	111.6 (3.2)	4.1 (-2.5, 10.8)	0.22

[a] Mean difference for continuous outcomes estimated from an analysis of covariance. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for blood glucose to millimoles per liter, multiply by 0.05551. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, SEM standard error of mean.