OLSTA-D
Randomized Clinical Trial

The efficacy and safety of OLOSTAR® in phaseⅢ clinical trial

2014-205 / OLST.140305

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PROTOCOL

PROTOCOL

Design	Multi-center, randomized, double-blind, double-dummy, placebo-controlled, factorial design, 4-arms				
Site	25 sites in Korea				
Coordinating Investigator	Hyo-soo Kim of Seoul National University Hospital				
Subjects	Mild to Moderate Hypertension & Dyslipidemia				
Arms	**OLOSTAR 40/20mg**	**OLOSTAR** + OMT 40mg placebo + RSV 20mg placebo			●□△
	OMT 40mg	OLOSTAR placebo + **OMT 40mg** + RSV 20mg placebo			○■△
	RSV 20mg	OLOSTAR placebo + OMT 40mg placebo + **RSV 20mg**			○□▲
	Placebo	OLOSTAR placebo + OMT 40mg placebo + RSV 20mg placebo			○□△
Schedule	**Visit 1 (≥-4 weeks)**	**Visit 2 (Week 0)**	**Visit 3 (Day 1)**	**Visit 4 (Week 4)**	**Visit 5 (Week 8)**
	Screening	Baseline	Randomization	Intermediate	Completion

OMT=Olmessartan, RSV=Rosuvastatin

INCLUSION CRITERIA

LDL-C and DBP are as follows in fasting state at the baseline visit.

Risk Factor*	10-year risk assessment	LDL-C (mg/dL)	DBP (mmHg)
0	-	≥160	90-109 (DM, CKD; 80-99)
≥1	<10%		
≥1	10~20%	≥130	
CHD or CHD equivalents**	>20%	≥100	

*** Risk factors**

① Smoking
② HDL-C<40 mg/dL
③ Family history of premature coronary artery disease
(development of coronary disease in men < 55 years and women < 65 years among parents or sibling)
④ Age (Men ≥ 45 and women ≥ 55)
[However, if HDL-C ≥ 60 mg/dL, subtracted one from total number of risk factors]

**** CHD equivalents**

: Carotid artery disease, peripheral vascular disease, abdominal aortic aneurysm, diabetes

LDL-C=Low Density Lipoprotein Cholesterol, DBP=Diastolic Blood Pressure, CHD=Coronary Heart Disease

EXCLUSION CRITERIA

1. Blood pressures measured at baseline visit (visit 2) and randomization visit (visit 3) were applicable to the standards of DBP ≥ 110 mmHg or SBP ≥180 mmHg

2. Known or suspected secondary hypertension/dyslipidemia

3. Severe heart disease
   Cerebrovascular disorder
   Autoimmune disease
   Chronic inflammatory condition
   Gastrointestinal disease
   Endocrine or metabolic disease

4. In relation to laboratory results

HbA1c	≥9%
FPG	≥160mg/dL
TSH	≥1.5 times of upper normal limit
Creatinine	≥1.5 times of upper normal limit
Ccr	<30mL/min
TG	≥400mg/dL
AST/ALT/CK	≥2 times of upper normal limit

DBP=Diastolic Blood Pressure, SBP= Systolic Blood Pressure, FPG=Fasting Plasma Glucose, TSH=Thyroid Stimulating Hormone, Ccr=Creatinine Clearance, TG=Triglyceride, AST=Aspartate Transaminase, ALT=Alanine Transaminase, CK=Creatine Kinase

EFFICACY EVALUATION

Lipid Parameter

1. % change & change from baseline in LDL-C · Total cholesterol and others after 4, 8 weeks
2. % of Subjects who achieved the goal of treatment in LDL-C defined by NCEP ATP III after 8 weeks

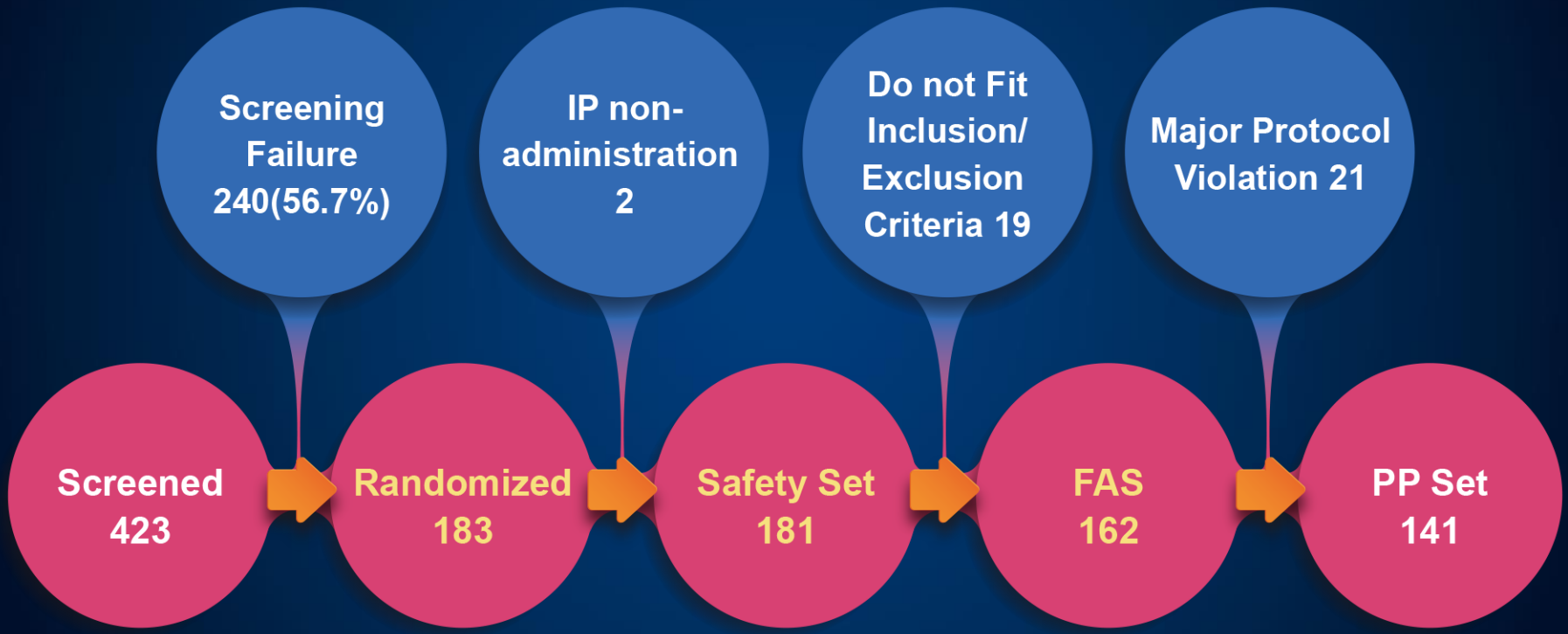
Blood Pressure

1. Change from baseline in DBP · SBP after 4, 8 weeks
2. % of Subjects who achieved the goal of treatment in BP defined by JNC 7 report after 8 weeks

SAFETY EVALUATION

1. Incidence of adverse events and adverse drug reaction
2. Abnormal vital signs and laboratory values
3. Abnormal physical exam, echocardiogram

SUBJECT DISPOSITION



IP=Investigational Product, FAS=Full Analysis Set, PP=Per Protocol

DEMOGRAPHIC

There were no significant differences in demographic characteristics among treatment groups

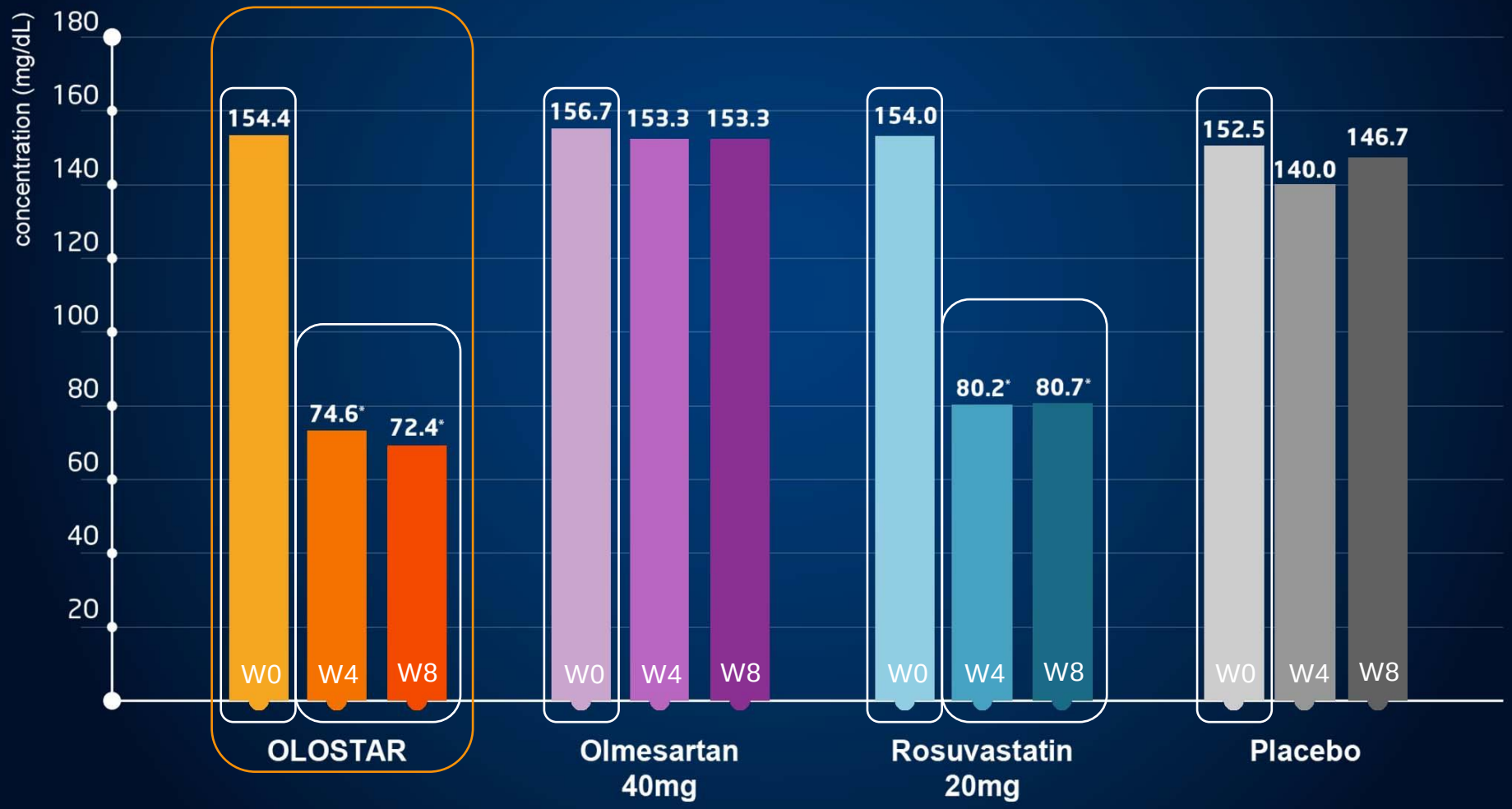
	OLOSTAR (N=61)	Olmesartan 40mg (N=36)	Rosuvastatin 20mg (N=36)	Placebo (N=29)	Total (N=162)	P-value*
Age (years)	61.9±8.1	59.5±6.9	61.8±8.0	62.5±8.2	61.4±7.8	0.4127
BMI (kg/m^2)	25.4±2.4	25.7±2.6	25.6±3.0	24.7±2.8	25.4±2.7	0.4580
Sex, n(%) Male Female	 34(55.7) 27(44.3)	 24(66.7) 12(33.3)	 25(69.4) 11(30.6)	 21(72.4) 8(27.6)	 104(64.2) 58(35.8)	0.3507
SBP (mmHg)	150.6±11.9	150.6±15.5	148.9±13.3	152.2±14.4	150.5±13.5	0.8109
DBP (mmHg)	92.0±7.4	93.3±5.0	92.9±6.5	92.5±7.0	92.6±6.6	0.8186
LDL-C (mg/dL)	154.4±32.2	156.7±34.5	154.0±28.2	152.5±32.7	154.5±31.7	0.9611
HDL-C (mg/dL)	48.9±10.8	52.1±12.3	50.7±12.0	48.6±11.1	50.0±11.4	0.3315
TG (mg/dL)	152.3±72.4	145.6±58.1	132.3±54.9	160.0±79.1	147.7±67.2	0.4643
TC (mg/dL)	230.5±37.6	233.3±38.2	227.4±32.3	228.9±37.0	230.2±36.2	0.9161

* Difference among treatment groups

EFFICACY
LIPID PARAMETER

1. Changes in LDL-C

OLOSTAR reduced LDL-C significantly at week 4 & week 8 compared with baseline.

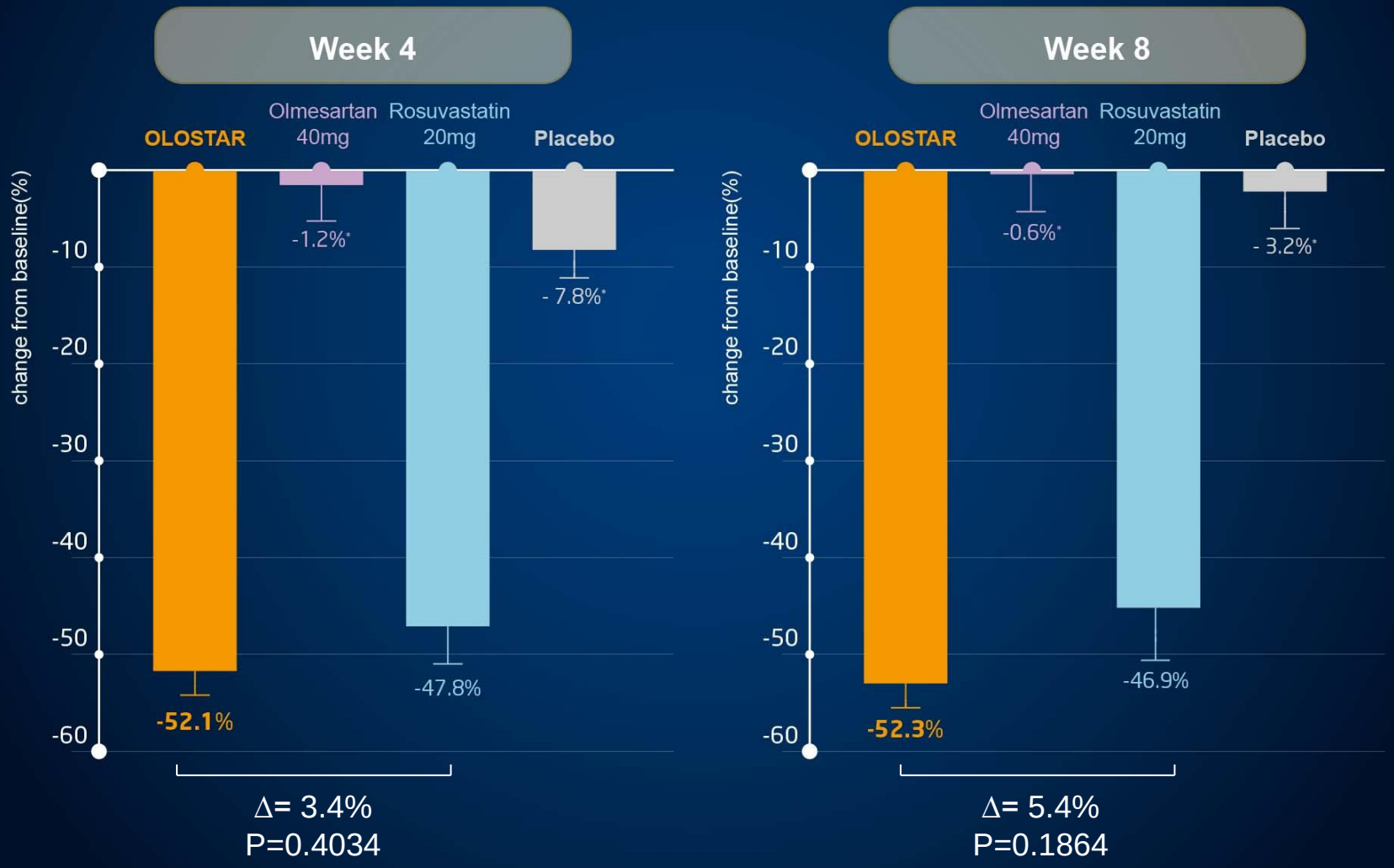


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with week 0)

1. % Change from Baseline in LDL-C

OLOSTAR reduced LDL-C as rosuvastatin 20mg.

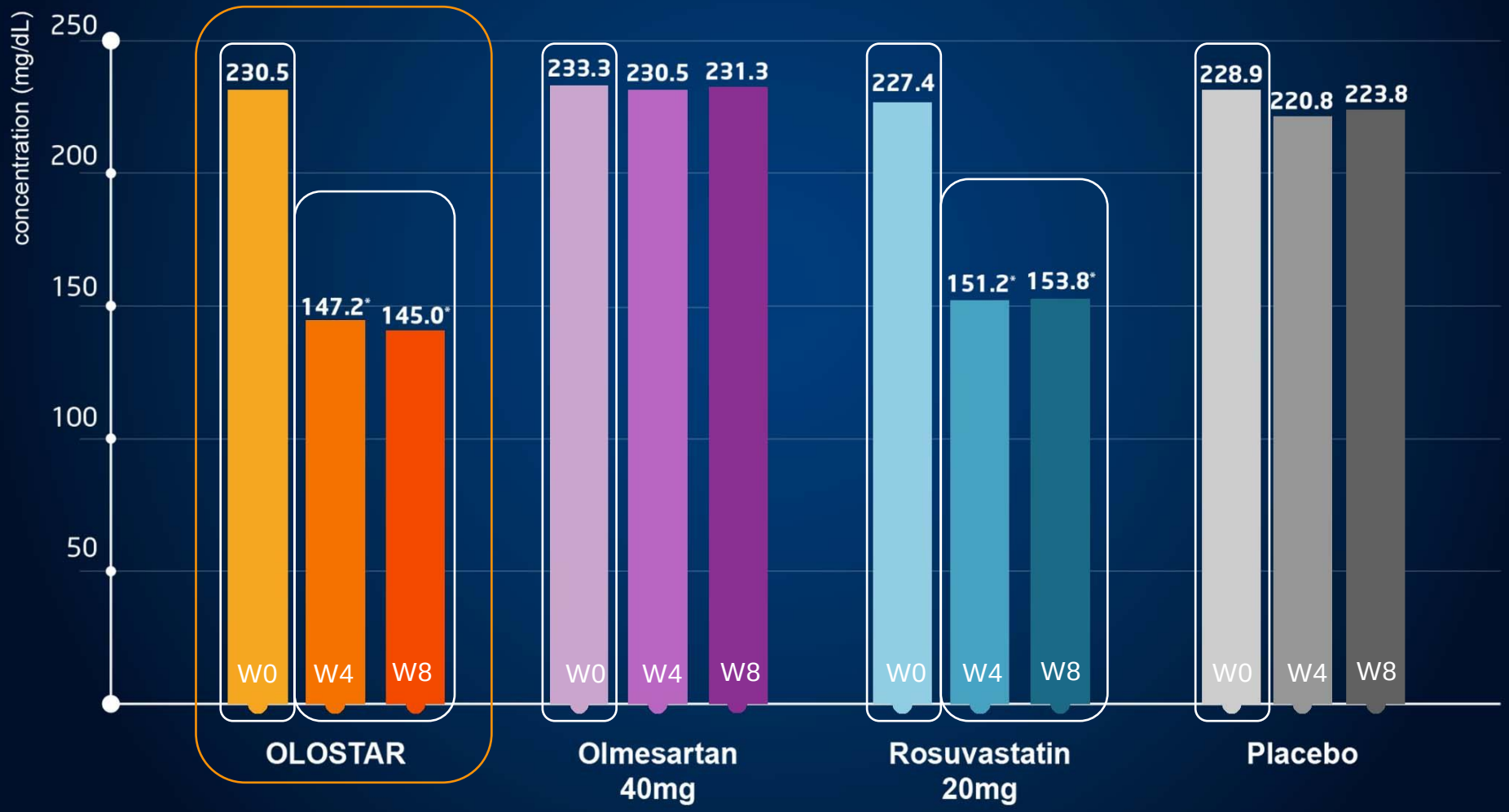


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001(comparing with OLOSTAR)

2. Changes in TC

OLOSTAR reduced total cholesterol significantly at week 4 & week 8 compared with baseline.

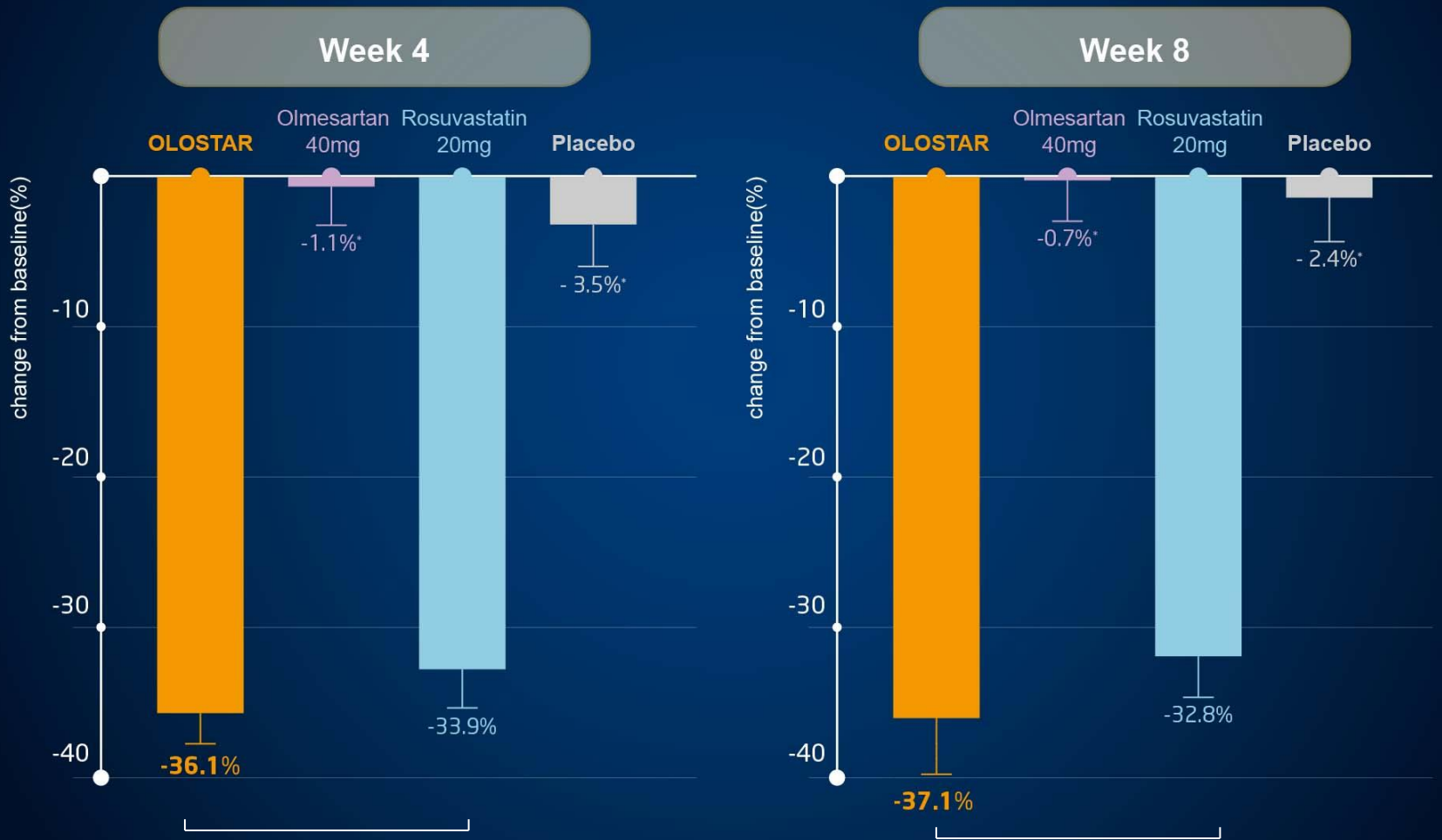


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with week 0)

2. % Change from Baseline in TC

OLOSTAR reduced total cholesterol as rosuvastatin 20mg.

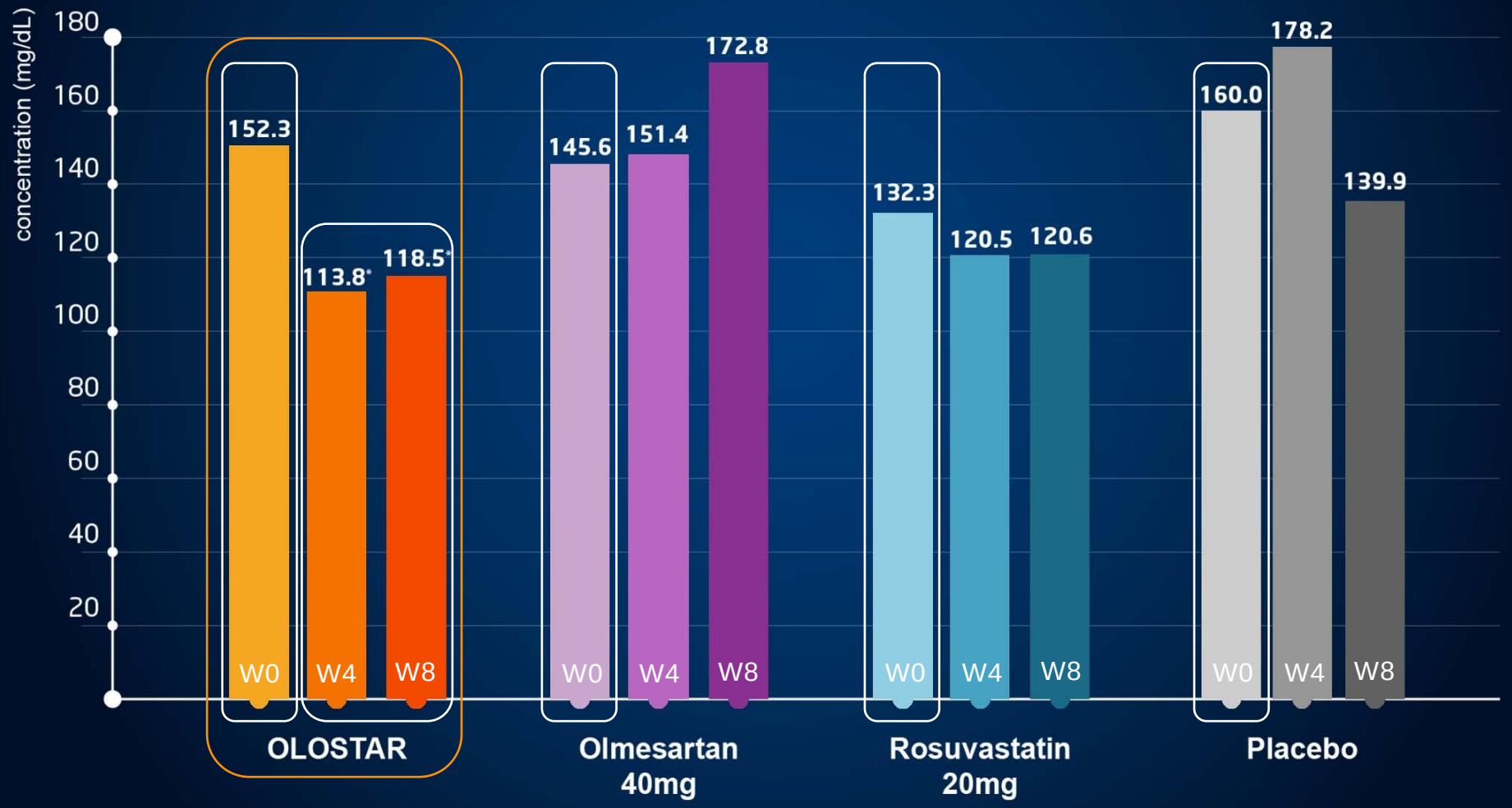


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001(comparing with OLOSTAR)

3. Changes in TG

OLOSTAR reduced triglyceride significantly at week 4 & week 8 compared with baseline.

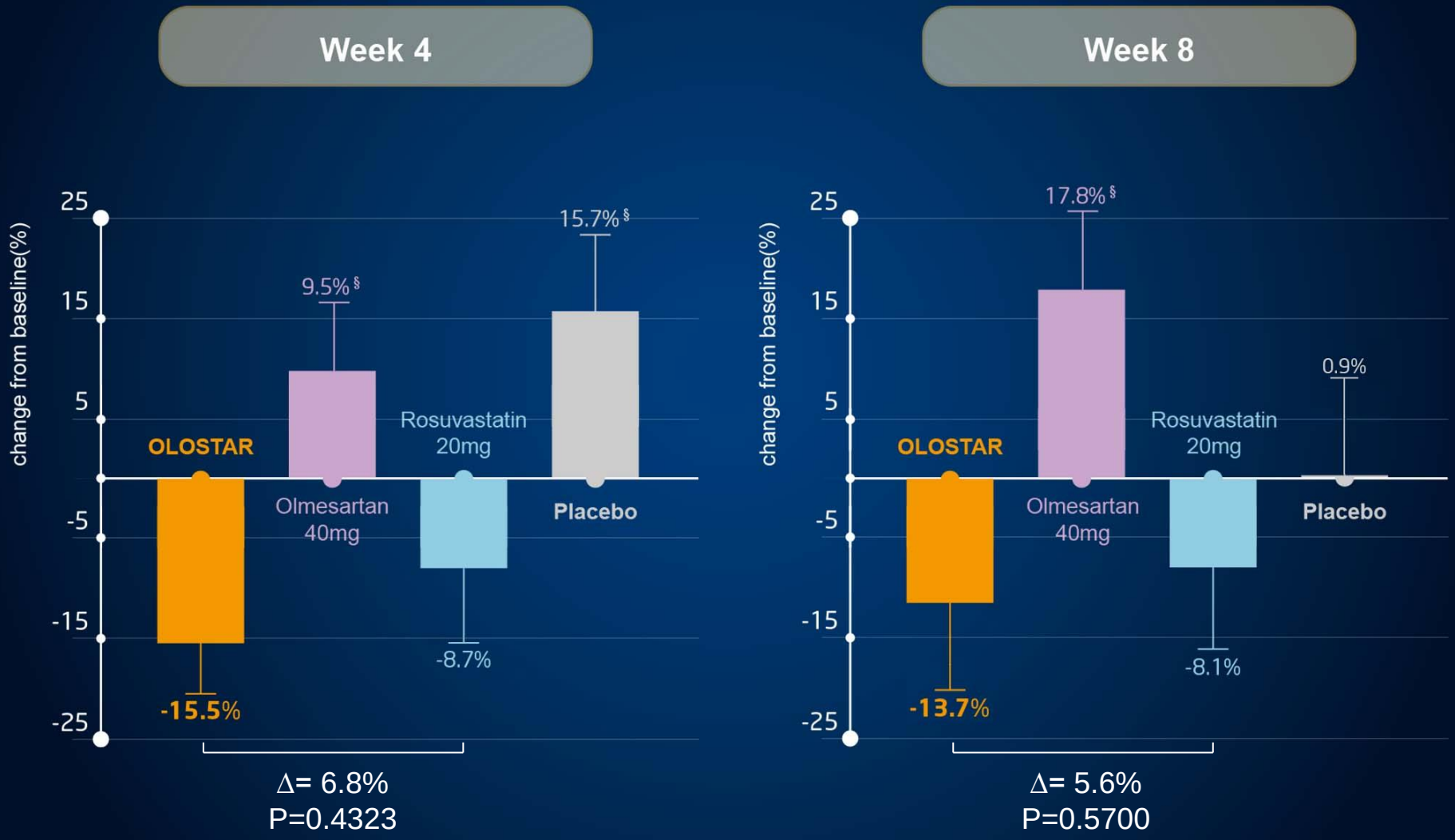


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with week 0)

3. % Change from Baseline in TG

OLOSTAR reduced triglyceride as rosuvastatin 20mg.

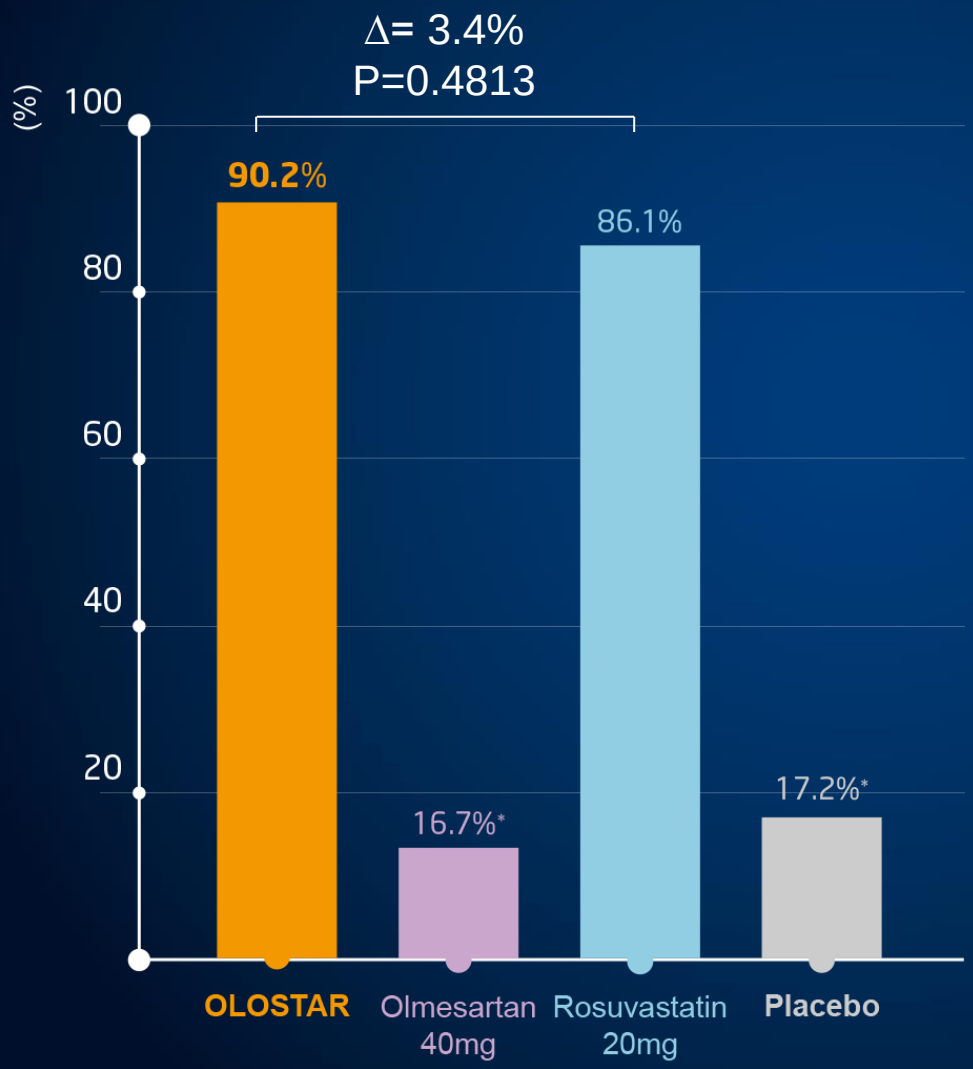


Ref.> Data on File. Daewoong. DW_DWJ1276003

§ p<0.05 (comparing with OLOSTAR)

4. % of Subject Who Achieved the Goal of Treatment in LDL-C at Week 8

OLOSTAR showed an excellent achievement of therapeutic goal defined by NCEP ATP III.



▪ Goal of Treatment by NCEP ATP III

Risk Factor	10yr risk assessment	Goal of Tx In LDL-C (mg/dL)
1	-	<160
≥2	<10%	<130
≥2	10~20%	
CHD or CHD equivalents	>20%	<100

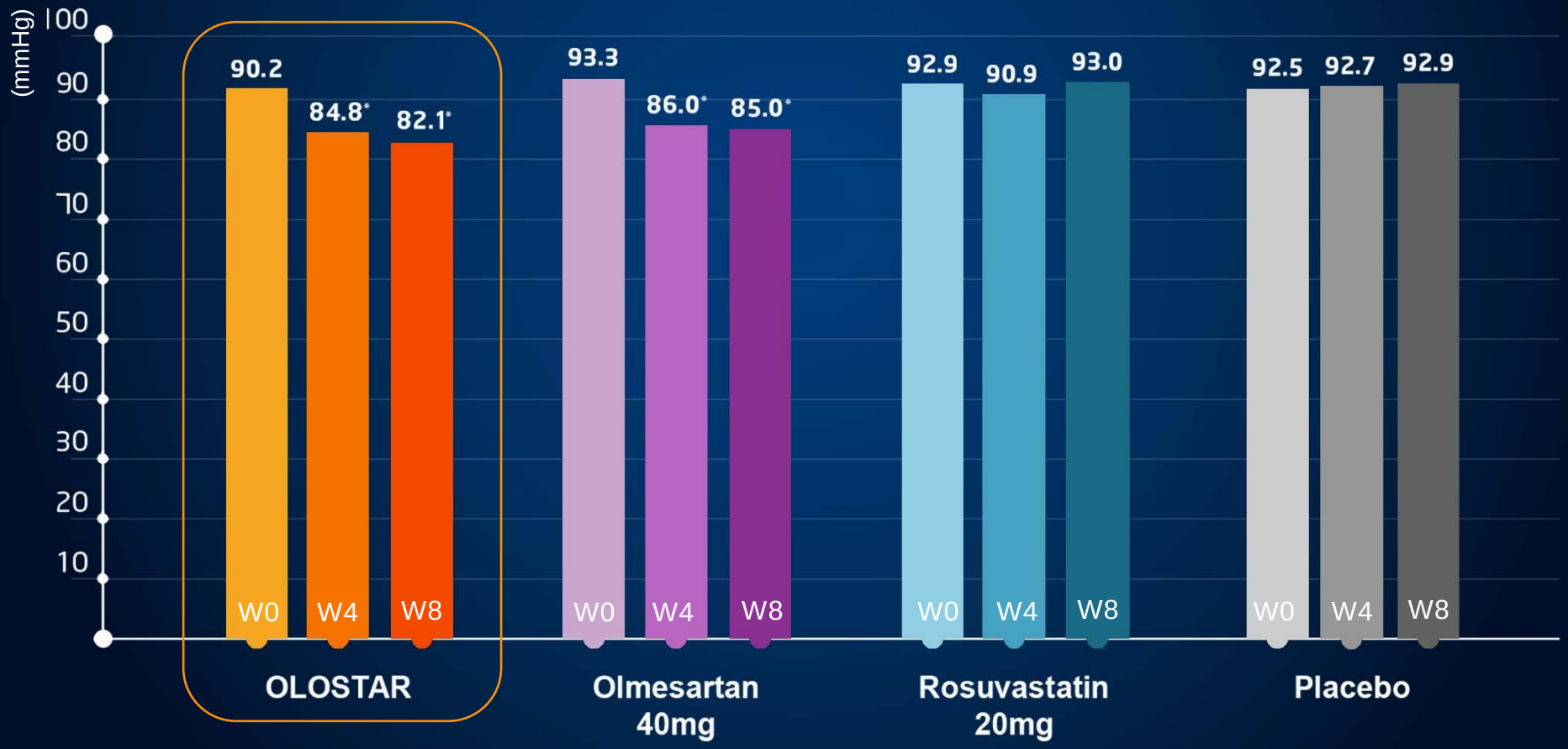
Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001(comparing with OLOSTAR)

EFFICACY
BLOOD PRESSURE

1. Changes in DBP

OLOSTAR reduced DBP significantly at week 4 & week 8 compared with baseline.

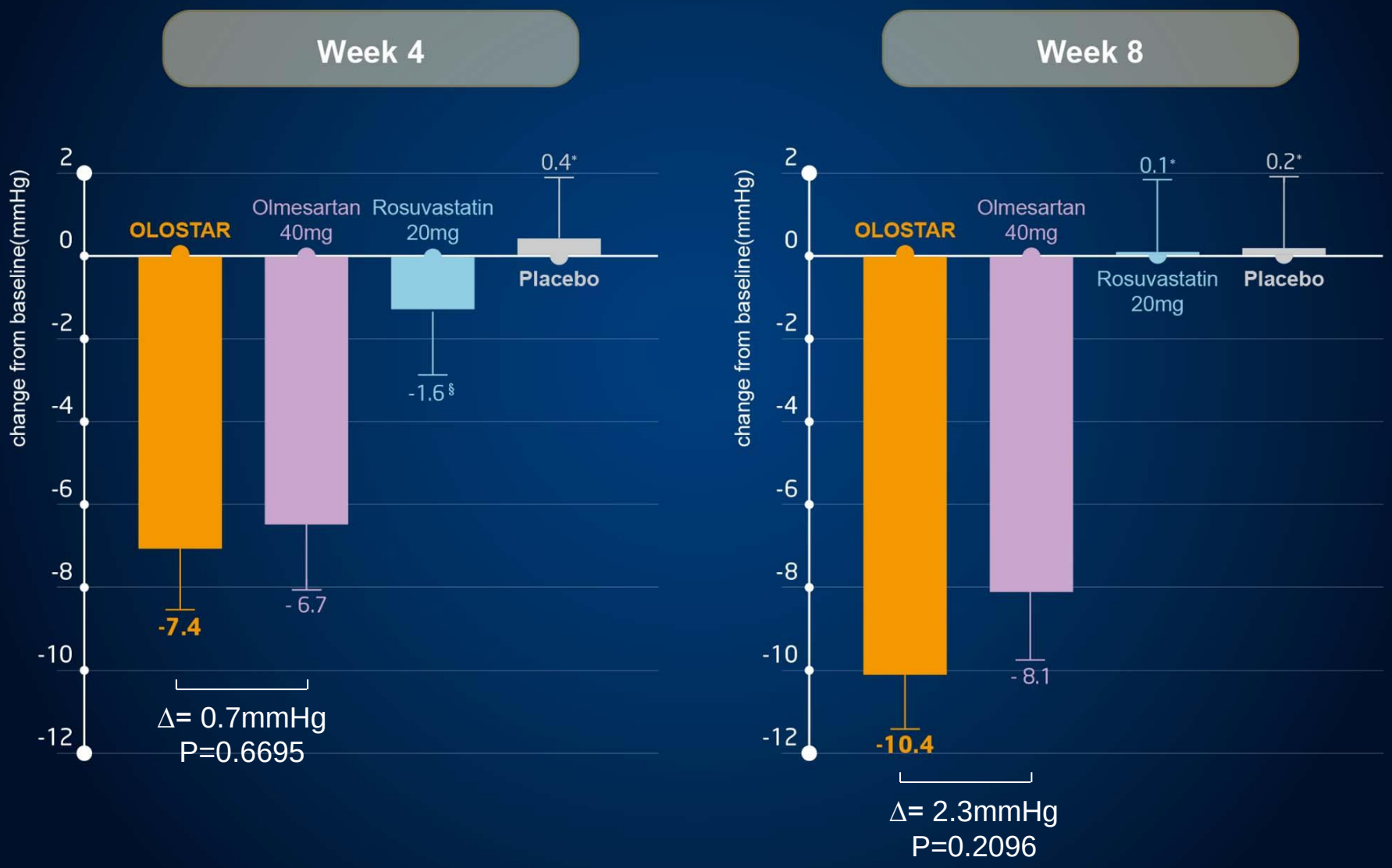


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with week 0)

1. Change from Baseline in DBP

OLOSTAR reduced diastolic blood pressure as olmesartan 40mg.

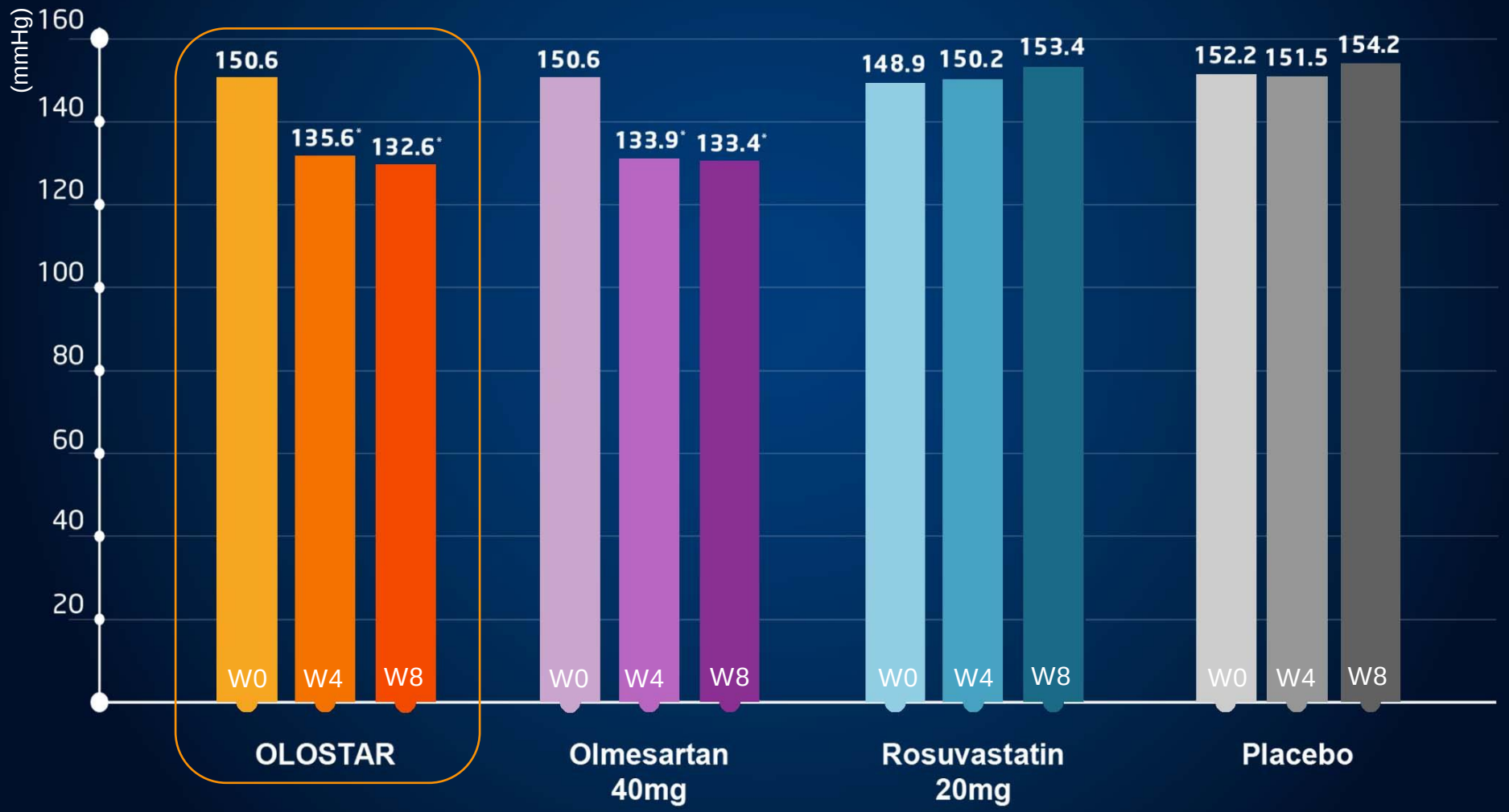


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001, § p<0.05(comparing with OLOSTAR)

2. Changes n SBP

OLOSTAR reduced SBP significantly at week 4 & week 8 compared with baseline.

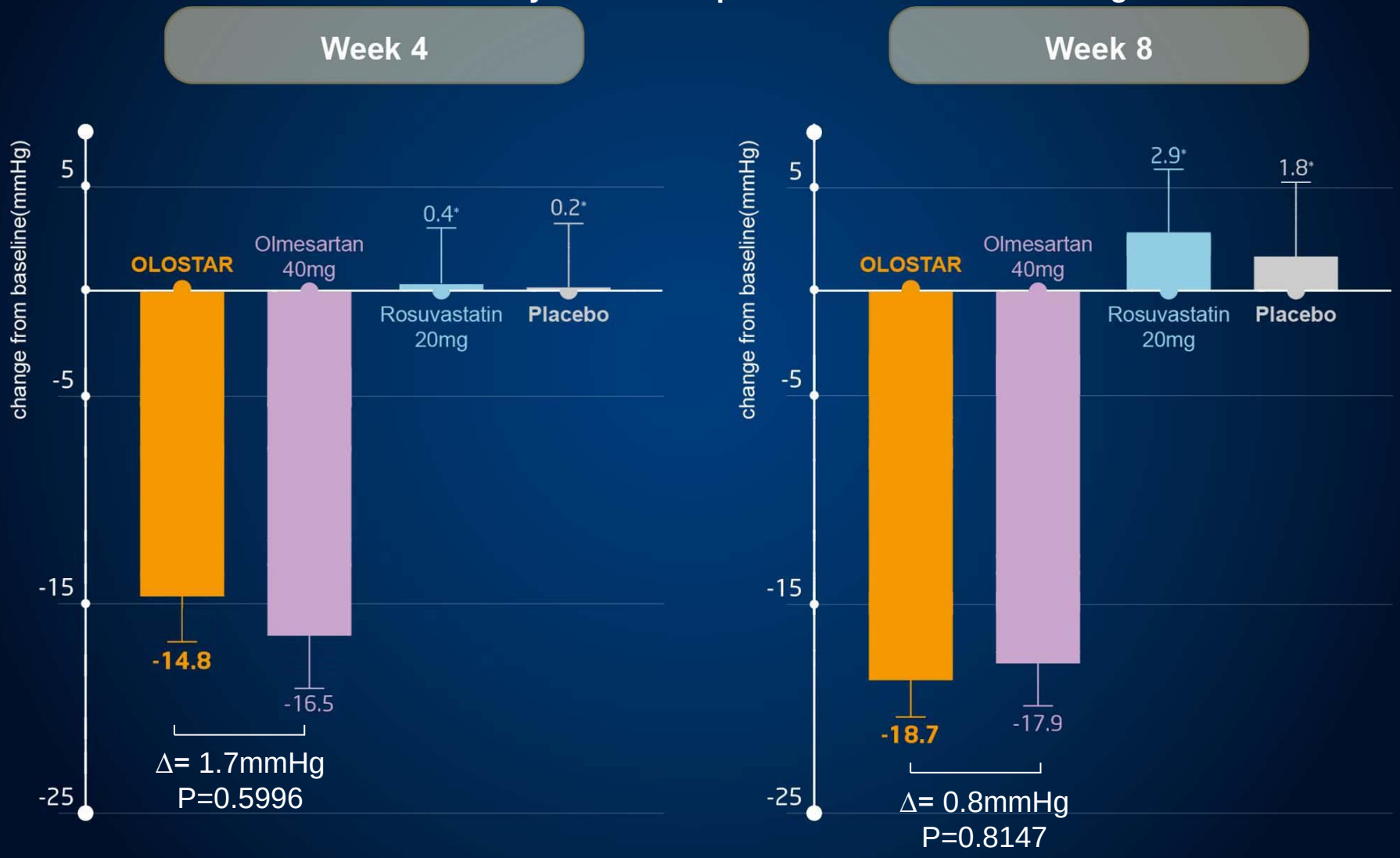


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with week 0)

2. Change from Baseline in SBP

OLOSTAR reduced systolic blood pressure as olmesartan 40mg.



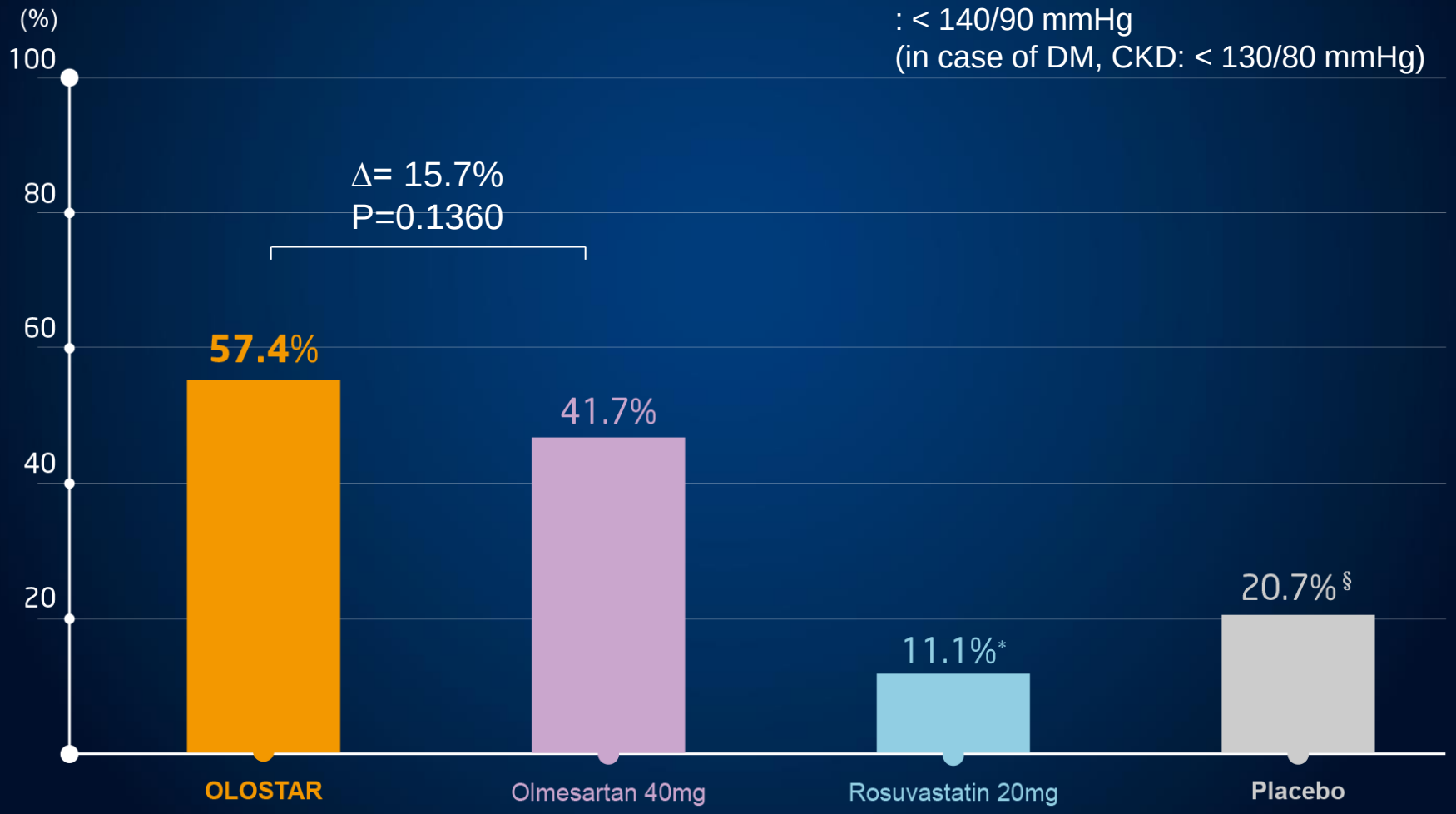
Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001(comparing with OLOSTAR)

3. % of Subject Who Achieved the Goal of Treatment defined by JNC7 in BP at Week 8

OLOSTAR showed an excellent achievement of therapeutic goal defined by JNC7.

- Goal of Treatment by JNC 7
  : < 140/90 mmHg
  (in case of DM, CKD: < 130/80 mmHg)

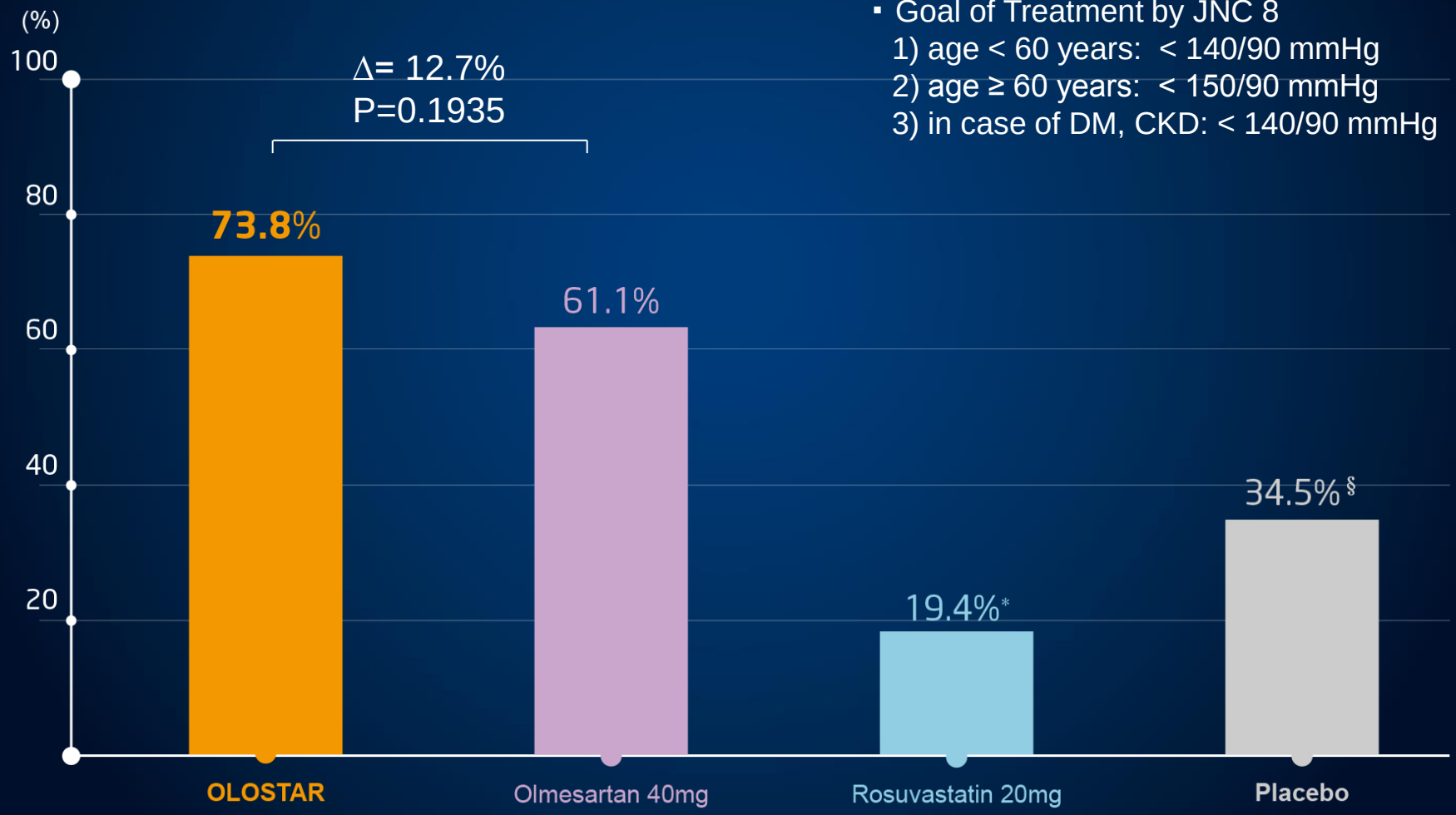


Ref.> Data on File. Daewoong. DW_DWJ1276003

* p<0.0001, § p<0.05(comparing with OLOSTAR)

4. % of Subject Who Achieved the Goal of Treatment defined by JNC8 in BP at Week 8

OLOSTAR showed an excellent achievement of therapeutic goal defined by JNC8.



- Goal of Treatment by JNC 8
  1) age < 60 years: < 140/90 mmHg
  2) age ≥ 60 years: < 150/90 mmHg
  3) in case of DM, CKD: < 140/90 mmHg

Ref.> Data on File. Daewoong

* p<0.0001, § p<0.05(comparing with OLOSTAR)

SAFETY

SUMMARY OF SAFETY

There were no significant differences in the incidence of AE/ADRs among treatment groups.

	OLOSTAR (N=71)	**Olmesartan 40mg** (N=38)	**Rosuvastatin 20mg** (N=38)	**Placebo** (N=38)	**Total** (N=181)
No. of AE P-value*	**24.9%** [17명, 23건]	**18.4%** [7명, 7건]	**23.7%** [9명, 11건]	**23.5%** [8명, 9건]	**22.7%** [41명, 50건] 0.9202
No. of ADR P-value*	**2.8%** [2명, 4건]	0	**5.3%** [2명, 3건]	**2.9%** [1명, 1건]	**2.8%** [5명, 8건] 0.5990
No. of SAE	0	2.6% [1명, 1건]	2.6% [1명, 1건]	0	1.1% [2명, 2건]
No. of Serious ADR	0	0	0	0	0

AE =Adverse Events, ADR =Adverse Drug Reactions, SAE=Serious Adverse Events
Ref.> Data on File. Daewoong. DW_DWJ1276003

* Difference among treatment groups

ADVERSE DRUG REACTION

All ADRs were expected side effects of approved drug.

	OLOSTAR (N=71)	Olmesartan 40mg (N=38)	Rosuvastatin 20mg (N=38)	Placebo (N=34)	Total (N=181)
ALT increased	1명(1.41%)[1건]	0	0	0	1명(0.55%)[1건]
AST increased	1명(1.41%)[1건]	0	0	0	1명(0.55%)[1건]
Creatinine increased	1명(1.41%)[1건]	0	0	0	1명(0.55%)[1건]
Ccr decreased	1명(1.41%)[1건]	0	0	0	1명(0.55%)[1건]
TG increased	0	0	0	1명(1.41%)[1건]	1명(0.55%)[1건]
Headache	0	0	2명(5.26%)[2건]	0	2명(1.10%)[2건]
Insomnia	0	0	1명(1.41%)[1건]	0	1명(0.55%)[1건]
Total	2명(2.82%)[4건]	0	2명(5.26%)[3건]	1명(2.94%)[1건]	**5명(2.76%)[8건]**

Ref.> Data on File. Daewoong. DW_DWJ1276003

SUMMARY

1. **OLOSTAR®** was highly effective to achieve the therapeutic goal of blood pressure and LDL-C.
   - **OLOSTAR®** was not different to Rosuvastatin 20mg in reducing LDL-C
   - **OLOSTAR®** was not different to Olmesartan 40mg in reducing blood pressure

2. **OLOSTAR®** was generally safe and well-tolerated.

CONCLUSION

OLOSTAR® can be recommended for the patients who have hypertension and dyslipidemia concomitantly.

OLOSTAR® would be a good therapeutic option for patients required to take both ARB and statin.