Efficacy and Tolerability of Continuous Release Formulation of Simvastatin (Simvast CR)

2010. 4. 17.

김상현, 조성욱, 현민수, 한규록, 서홍석, 김영권, 박성훈

고지혈증 환자에서 심바스트 CR의 복용시점에 따른 유효성 및 내약성을 평가하기 위한 비교, 이중눈가림, 무작위배정, 다기관 공동 제 3상 임상시험

Pharmacokinetic properties of the statins

	Rosuvastatin	Pitavsatatin
Opitmal time of dosing	Any time of day	Any time of day
Bioavailability(%)	20	80
Solubility	Hydrophilic	Lipophilic
Effect of food	No effect	Not available
Protein binding(%)	90	96
Active metabolites	Minor	Minor
Elimination half-life(h)	19	11
CYP450 metabolism and isoenzyme	Limited	Limited
Renal excretion(%)	(2C9, 2C19, 1A2, 2D6, 2E1)	Glucuronidation
	10	

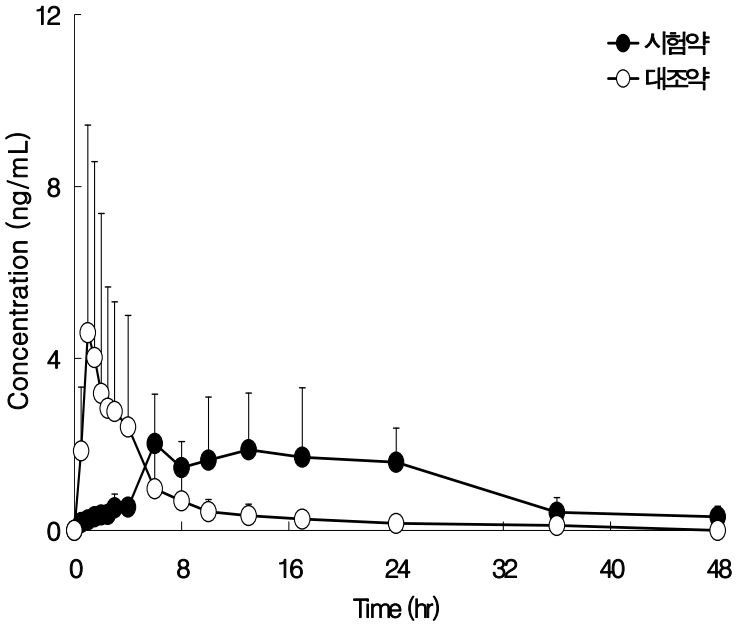
Characteristics of Statins

Characteristic	Lovastatin	Pravastatin	Simvtastin	Atorvastatin	Fluvastatin	Cerivastatin
Maximal dose (mg/day)	80	40	80	80	40	0.3
Maximal serum LDL cholesterol reduction produced (%)	40	34	47	60	24	28
Serum LDL cholesterol reduction produced (%)	34	34	41	50	24	28
Serum triglyceride reduction produced (%)	16	24	18	29	10	13
Serum HDL cholesterol increase	8.6	12	12	6	8	10
Plasma half-life(hr)	2	1-2	1-2	14	1.2	2-3
Effect of food on absorption of drug absorption absorption	Increased	Decreased	None	None	Negligible	None
Optimal time of administration	With meals (morning and evening)	Bedtime	Evening	Anytime	Bedtime	Evening
Penetration of central nervous system	Yes	No	Yes	No	No	Yes
Renal excretion of absorbed dose	10	20	13	2	<6	33
Mechanism of hepatic metabo-lism	Cytochrome P-450 3A4	Sulfation	Cytochrome P-450 3A4	Cytochrome P-450 3A4	Cytochrome P-450 2C9	Cytochrome P-450 3A4, 2C8

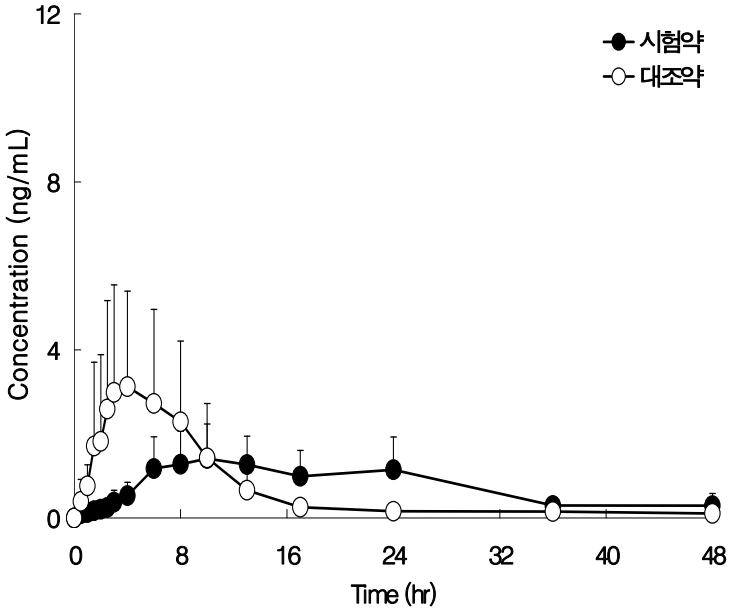
Wood AJ. NEJM 1999;341(7):498-511

Pharmacokinetic Profile

- 심바스타틴의 혈중 농도



- 심바스타틴산의 혈중 농도



시험약 : Simvast CR

대조약 : Zocor

임상연구 목적

고지혈증 환자에서 Simvast CR 20 mg

아침복용과 저녁복용의 경우에 따른

효과와 내약성을 비교

연구자

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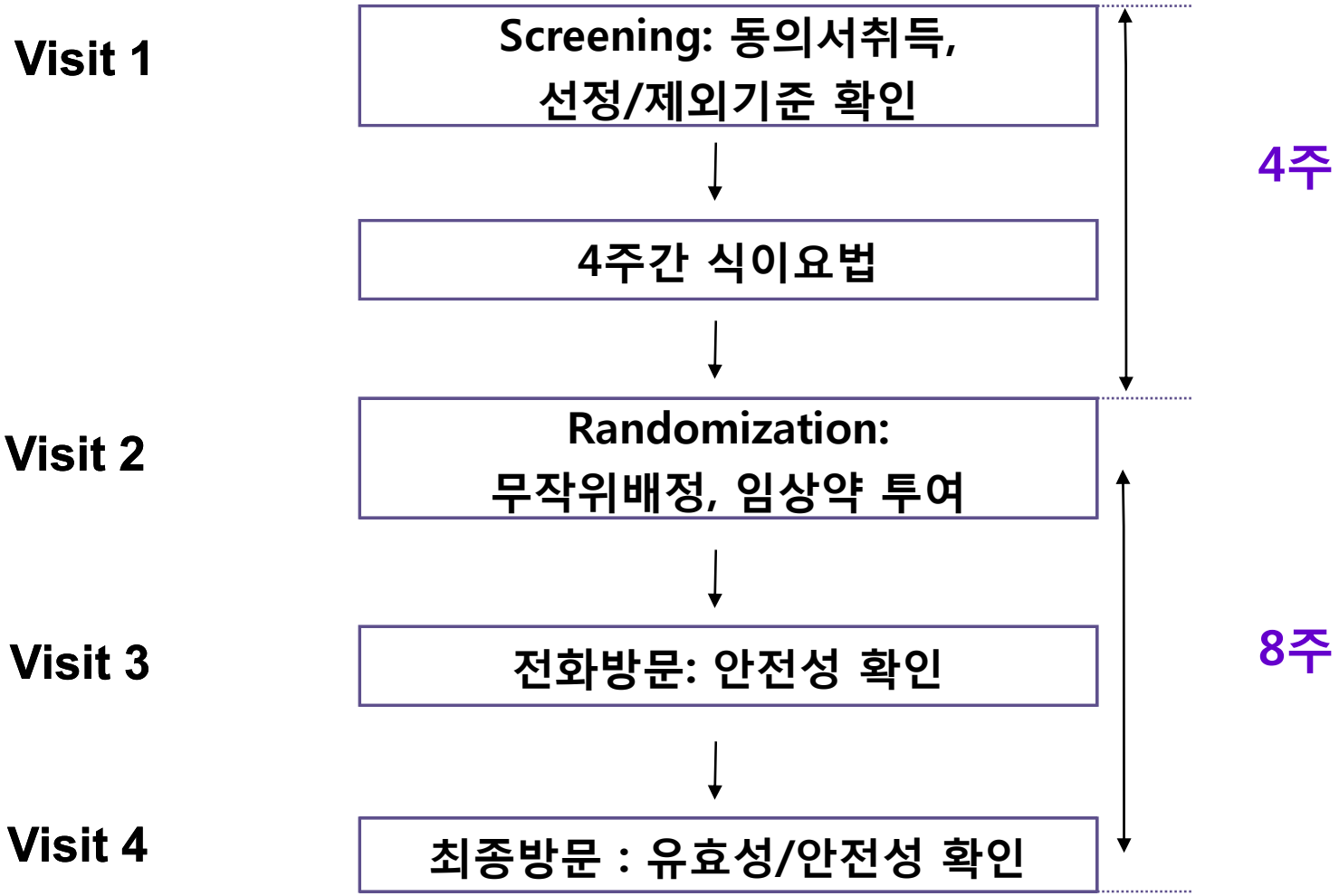
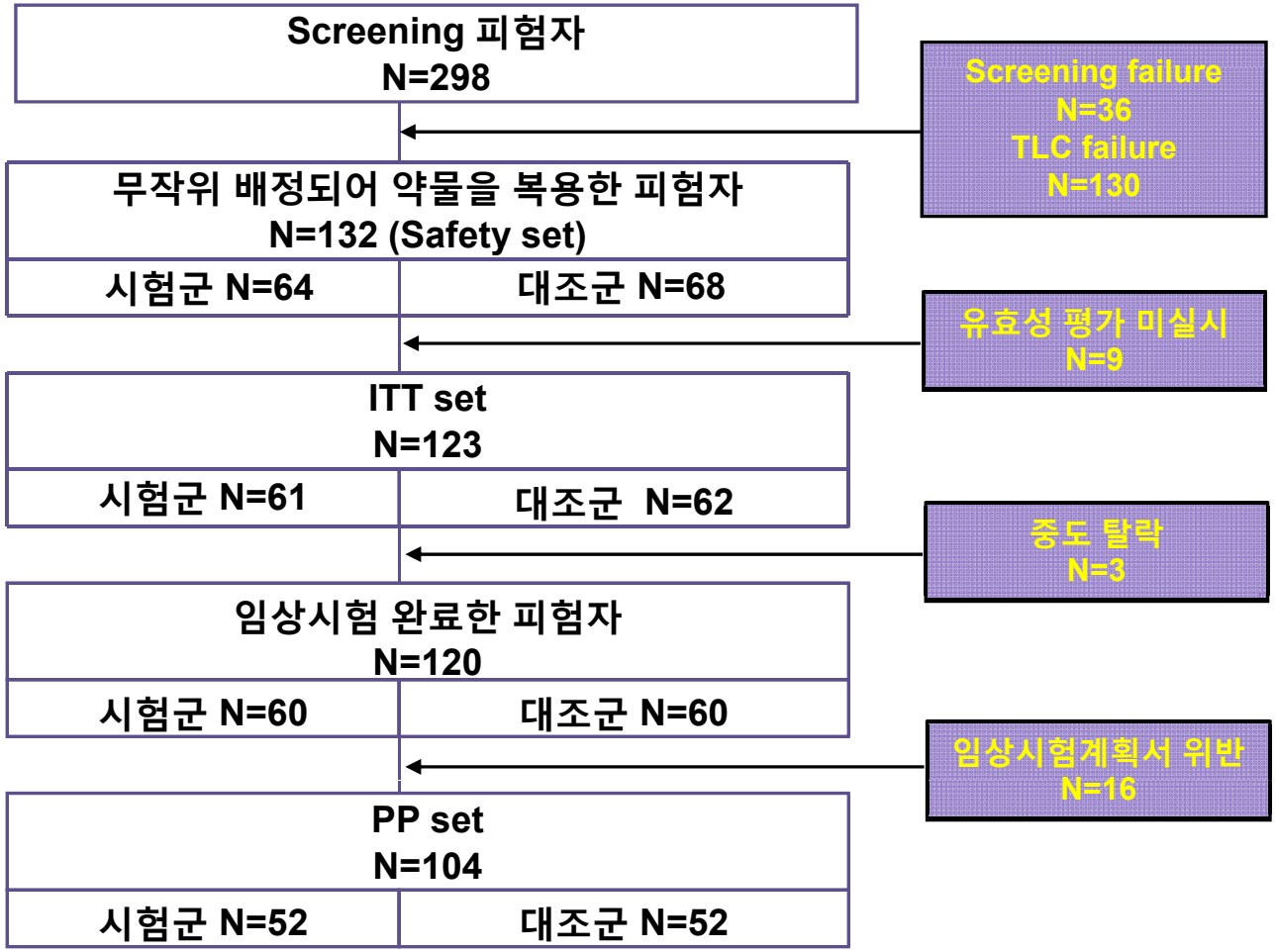
순천향대학교 의과대학 부속병원	현민수
한림대학교 강동성심병원	한규록

임상시험 FLOW


Visit 1
Screening: 동의서취득,
선정/제외기준 확인
4주간 식이요법
Visit 2
Randomization:
무작위배정, 임상약 투여
Visit 3
전화방문: 안전성 확인
Visit 4
최종방문 : 유효성/안전성 확인
4주
8주

Study Flow



※시험군: Simvast CR 아침 복용군 ※ 대조군: Simvast CR 저녁 복용군

Baseline Characteristics (1)

❖ 인구학적 정보 : ITT set

항목	구분	시험군 (N=61)	대조군 (N=62)	P-Value
성별 (명(%))	남자	26 (42.62)	29 (46.77)	0.6434
	여자	35 (57.38)	33 (53.23)	
연령 (세)	Mean±SD	58.7 ± 8.3	58.5 ± 9.5	0.8908
	Min-Max	36-75	39-81	
체중 (㎏)	Mean±SD	66.1 ± 10.9	66.6 ± 9.5	0.7934
	Min-Max	40.5-91	50.4-91.7	
수축기혈압 (mmHg)	Mean±SD	129.8 ± 15.4	126.7 ± 13.9	0.2420
	Min-Max	100-159	94-156	
이완기혈압 (mmHg)	Mean±SD	81.1 ± 8.9	81.1 ± 10.2	0.9934
	Min-Max	60-100	58-100	

Baseline Characteristics (2)

❖ CHD Risk Assessment : ITT set

	시험군 (N=61)		대조군 (N=62)		P-value
	N	(%)	N	(%)	
CHD or CHD risk equivalent (10-year risk >20%)	32	(52.46)	34	(54.84)	0.3437
2 or more risk factors (10%≤10-year risk≤20%)	16	(26.23)	10	(16.13)	
2 or more risk factors (10-year risk<10%)	6	(9.84)	5	(8.06)	
0 to 1 risk factor	7	(11.48)	13	(20.97)	

유효성 결과

Primary parameter (1)

❖ LDL-C 변화율: ITT set

단위 : mg/dL, %

T-test / ANCOVA		시험군 (N=61)	대조군 (N=62)
Primary analysis			
Baseline (mg/dL)	Mean ± SD	155.0± 22.3	160.6± 25.0
Week8	Mean ± SD	98.9± 23.7	98.3± 21.6
Difference	Mean ± SD	-56.1± 25.8	-62.3± 22.7
Within Group p-value		<.0001*	<.0001*
Between Group	Mean ± SD(95% CI)	-6.21± 24.28(-14.89, 2.46)	
	p-value	0.1584	
Percent change	Mean ± SD	-35.7± 15.6	-38.5± 11.5
Within Group p-value		<.0001*	<.0001*
Between Group	Mean ± SD(95% CI)	-2.78± 13.66(-7.65, 2.10)	
	p-value	0.2634	

*Statistically significant difference

Secondary parameter(1)

❖ LDL-C의 변화율 : PP set

단위 : mg/dL, %

T-test / ANCOVA		시험군 (N=52)	대조군 (N=52)
Primary analysis			
Baseline	Mean ± SD	155.6± 23.3	160.9± 25.8
Week8	Mean ± SD	96.1± 21.9	96.0± 20.2
Difference	Mean ± SD	-59.4± 22.6	-65.0± 21.3
Within Group p-value		<.0001*	<.0001*
Between Group	Mean ± SD(95% CI)	-5.53± 21.93(-14.06, 3.01)	
	p-value	0.2018	
Percent change	Mean ± SD	-37.9± 12.7	-40.0± 10.2
Within Group p-value		<.0001*	<.0001*
Between Group	Mean ± SD(95% CI)	-2.16± 11.55(-6.65, 2.33)	
	p-value	0.3420	

*Statistically significant difference

Secondary parameter (2)

❖ TC, TG 변화량 및 변화율 : ITT set

단위 : mg/dL, %

			시험군 (N=61)	대조군 (N=62)
TC	Baseline		234.0± 28.9	238.4± 31.1
	Week8		173.7± 31.1	171.9± 29.1
	Difference	Mean ± SD	-62.3± 28.5	-66.5± 27.3
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-4.22± 27.87(-14.17, 5.73)	
		p-value	0.4026	
	Percent Change	Mean ± SD	-26.2± 11.6	-27.6± 10.0
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-1.44± 10.84(-5.31, 2.43)	
		p-value	0.4634	
TG	Baseline		157.1± 65.2	147.3± 63.1
	Week8		130.3± 65.2	125.3± 64.9
	Change	Mean ± SD	-26.8± 61.0	-22.0± 73.9
	Within Group p-value		0.0011*	0.0224*
	Between Group	Mean ± SD(95% CI)	4.82± 67.81(-19.39, 29.03)	
		p-value	0.6942	
	Percent Change	Mean ± SD	-12.4± 35.8	-7.3± 46.4
	Within Group p-value		0.0089*	0.2207
	Between Group	Mean ± SD(95% CI)	5.09± 41.47(-9.71, 19.90)	
		p-value	0.4964	

*Statistically significant difference

Secondary parameter (3)

❖ HDL-C, Apo AI 변화량 및 변화율 : ITT set

단위 : mg/dL, %

			시험군 (N=61)	대조군 (N=62)
HDL-C	Baseline		48.6± 9.7	50.3± 11.3
	Week8		53.2± 10.9	55.6± 12.3
	Difference	Mean ± SD	4.6± 7.5	5.3± 8.2
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	0.67± 7.81(-2.12, 3.46)	
		p-value	0.6333	
	Percent Change	Mean ± SD	10.5± 16.0	11.8± 17.0
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	1.22± 16.53(-4.68, 7.12)	
		p-value	0.6835	
Apo AI	Baseline		141.9± 21.4	145.7± 24.0
	Week8		155.2± 24.6	157.3± 25.4
	Change	Mean ± SD	13.3± 18.3	11.6± 22.4
	Within Group p-value		<.0001*	0.0001*
	Between Group	Mean ± SD(95% CI)	-1.76± 20.45(-9.07, 5.54)	
		p-value (b)	0.6334	
	Percent Change	Mean ± SD	10.1± 13.4	9.1± 15.7
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-1.04± 14.59(-6.25, 4.17)	
		p-value (b)	0.6933	

*Statistically significant difference

Secondary parameter (4)

❖ Apo B, Lipoprotein(α) 변화량 및 변화율 : ITT set

단위 : mg/dL, %

			시험군 (N=61)	대조군 (N=62)
Apo B	Baseline		106.0± 16.7	110.0± 16.0
	Week8		74.4± 16.0	73.5± 17.4
	Change	Mean ± SD	-31.6± 17.6	-36.5± 17.4
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-4.91± 17.51(-11.16, 1.34)	
		p-value	0.1227	
	Percent Change	Mean ± SD	-29.0± 16.0	-32.8± 14.0
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-3.85± 14.99(-9.20, 1.50)	
		p-value	0.1571	
Lp(α)	Baseline		21.4± 21.2	29.0± 22.3
	Week8		19.4± 18.5	27.98± 24.9
	Change	Mean ± SD	-1.9± 8.1	-1.0± 10.5
	Within Group p-value		0.0705	0.4386
	Between Group	Mean ± SD(95% CI)	0.87± 9.37(-2.47, 4.22)	
		p-value	0.6059	
	Percent Change	Mean ± SD	-6.0±36.2	-3.0± 48.9
	Within Group p-value		0.2064	0.6365
	Between Group	Mean ± SD(95% CI)	3.02±159.70(-12.45, 18.49)	
		p-value)	0.6987	

*Statistically significant difference

Secondary parameter (5)

❖ LDL-C/HDL-C Ratio, Apo B/Apo AI Ratio: ITT set

			시험군 (N=61)	대조군 (N=62)
LDL-C /HDL-C Ratio	Baseline		3.28± 0.72	3.30± 0.72
	Week8		1.93± 0.58	1.84± 0.56
	Change	Mean ± SD	-1.36± 0.58	-1.46± 0.55
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-0.11± 0.57(-0.31, 0.10)	
		p-value	0.2994	
	Percent Change	Mean ± SD	-41.19± 13.77	-44.04± 11.88
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-2.85± 12.85(-7.44, 1.74)	
		p-value	0.2207	
Apo B /Apo AI Ratio	Baseline		0.76± 0.16	0.77± 0.16
	Week8		0.49± 0.13	0.48± 0.14
	Change	Mean ± SD	-0.27± 0.13	-0.30± 0.13
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-0.02± 0.13(-0.07, 0.02)	
		p-value	0.3361	
	Percent Change	Mean ± SD	-35.13± 13.83	-37.85± 13.26
	Within Group p-value		<.0001*	<.0001*
	Between Group	Mean ± SD(95% CI)	-2.73± 13.55(-7.56, 2.11)	
		p-value	0.2669	

*Statistically significant difference

Secondary parameter (6)

❖ LDL-C 치료목표 달성율: ITT set

Risk category	도달여부	시험군 (N=61) N	(%)	대조군 (N=62) N	(%)	Between Group p-value
CHD or CHD risk equivalent (10-year risk > 20%)	예	21	(65.63)	20	(58.82)	0.5692
	아니오	11	(34.38)	14	(41.18)	
2 or more risk factors (10%≤10-year risk≤20%)	예	14	(87.50)	10	(100.00)	0.5077
	아니오	2	(12.50)	0	(0.00)	
2 or more risk factors (10-year risk<10%)	예	4	(66.67)	4	(80.00)	1.0000
	아니오	2	(33.33)	1	(20.00)	
0 to 1 risk factor	예	7	(100.0)	13	(100.00)	-
	아니오	0	(0.00)	0	(0.00)	
Percent to achieve target goals	예	46	(75.41)	47	(75.81)	0.9592
	아니오	15	(24.59)	15	(24.19)	

Secondary parameter (5)

❖ Non HDL-C 목표치 달성율 : ITT set

Risk category	도달여부	시험군 (N=61) N	(%)	대조군 (N=62) N	(%)	Between Group p-value
CHD or CHD risk equivalent (10-year risk > 20%)	예	24	(75.00)	29	(85.29)	0.2933
	아니오	8	(25.00)	5	(14.71)	
2 or more risk factors (10%≤10-year risk≤20%)	예	13	(81.25)	10	(100.00)	0.2615
	아니오	3	(18.75)	0	(0.00)	
2 or more risk factors (10-year risk<10%)	예	4	(66.67)	4	(80.00)	1.0000
	아니오	2	(33.33)	1	(20.00)	
0 to 1 risk factor	예	7	(100.0)	13	(100.00)	-
	아니오	0	(0.00)	0	(0.00)	
Percent to achieve target goals	예	48	(78.69)	56	(90.32)	0.0743
	아니오	13	(21.31)	6	(9.68)	

안전성 평가 결과

Compliance

❖ Compliance : Safety set

Compliance(%)	시험군 (N=64)	대조군 (N=68)	Total (N=132)	p-value
Baseline ~ Week 8				
아침약				0.8979
N	63 †	66 ‡	129	
Mean±SD	93.44±12.37	93.73±13.11	93.58±12.71	
저녁약				0.6154
N	63 ‡	66 †	129	
Mean±SD	89.61±12.97	90.88±13.66	90.26±14.27	
아침약-저녁약				-
Mean±SD	3.82±6.43	2.84±8.20	3.32±7.38	
p-value	<.0001*	0.0064*	<.0001*	
전체				0.9350
N	63	66	129	
Mean±SD	91.52±13.35	92.30±12.74	91.92±13.00	

† Simvast CR

‡ Placebo

Adverse Events (1)

❖ Summary of adverse events : Safety set

이상반응		시험군 (N=64)	대조군 (N=68)	p-value
		n(%) [건]	n(%) [건]	
임상약 투여 전		5(7.81) [5]	3(4.41) [3]	0.4831
90% Exact C.I		(0.8427 , 0.9687)	(0.8899 , 0.9879)	
임상약 투여 후 †		20(31.25) [25]	21(30.88) [30]	0.9636
90% Exact C.I		(0.5791 , 0.7823)	(0.5865 , 0.7828)	
		n(%)	N(%)	
중대한 이상반응 †		1(1.56)	1(1.47)	1.0000
이상반응의 중증도 †	Mild	16(25.00)	19(27.94)	-
	Moderate	4(6.25)	2(2.94)	
	Severe	0(0.00)	0(0.00)	
중도탈락의 원인이 된 이상반응 †		2(3.13)	4(5.88)	0.6811
임상약과 관련 있는 이상반응 †		5(7.81)	4(5.88)	0.7839
사망		-	-	-

† Treatment-emergent adverse event

Adverse Events (2)

❖ Treatment related Adverse Events: Safety set

이상반응*	시험군 (N=64)		대조군 (N=68)	
	n	(%)	n	(%)
Gastrointestinal disorders	5	(7.81)	2	(2.94)
Constipation	3	(4.69)	0	(0.00)
Dyspepsia	2	(3.13)	1	(1.47)
Musculoskeletal and connective tissue disorders	0	(0.00)	2	(2.94)

Summary and Conclusion

- 고지혈증 환자에서 Simvast CR 20mg을 8주 동안 아침에 복용한 시험군과 저녁에 복용한 대조군을 비교
  - 양 군 모두 효과적으로 LDL cholesterol의 감소
- 이상반응에 있어서 유의한 차이가 없었음
- 양 군 모두 아침 복용이 저녁 복용 보다 좋은 compliance를 보임
- Simvast CR 20mg을 아침에 복용하는 것은 저녁 복용과 비슷한 효과를 보여 치료적 유용성이 있다고 평가됨

THANK YOU