

# Rupatadine : Novel Antihistamine for the Treatment of Allergic Disease

서울의대 보라매 병원

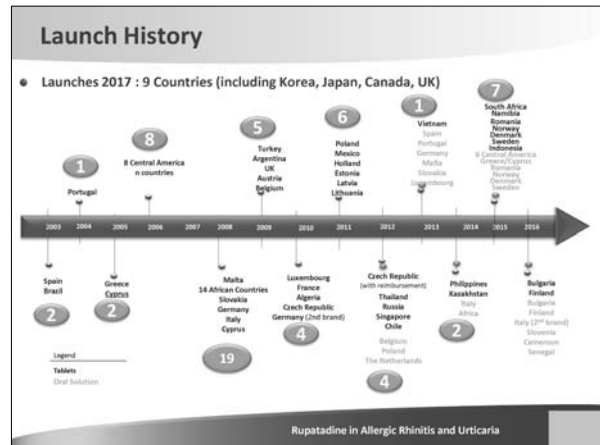
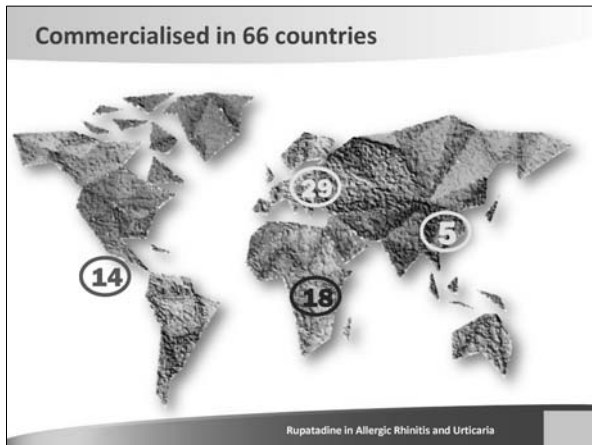
김 대 우



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- Introduction
- **Rupatadine International Status**
- Pharmacology of Rupatadine
- Rupatadine in Allergic rhinitis & Urticaria
- Safety and Tolerability of Rupatadine
- Conclusions

Rupatadine in Allergic Rhinitis and Urticaria



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## Pharmacological properties of the ideal oral antihistamine

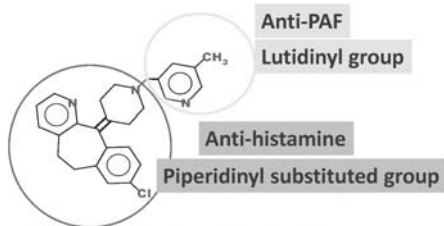
- Potent and selective H<sub>1</sub> receptor blockade
- Additive antiallergic activities
- No clinically relevant interference by foods or medications
- Rapid onset and long duration of action
- No sedation

Bouquet L, et al. Allergy. 2003;58:152-7.  
Bouquet L, et al. Allergy. 2006;61:1390-96.  
Bouquet L, et al. Allergy. 2006;61(Suppl 8):S-160.

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## Chemical structure of rupatadine

Rupatadine (fumarate) C<sub>26</sub>H<sub>26</sub>Cl N<sub>3</sub>·C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

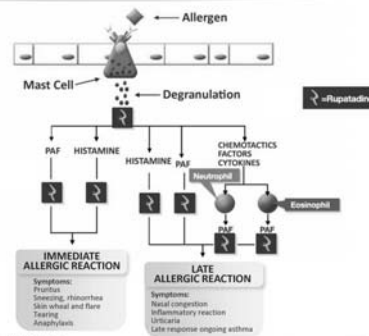


Dual inhibitor of histamine and PAF induced effects

Carstoffer E. J Med Chem. 1994;37:2637-703.  
Picolo C. Expert Opin Pharmacother. 2006;7:1989-2001.  
Keam SS. Drugs. 2007;67:457-74.  
J. Med Chem 1994, 37: 2637-2703

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## Mechanism of action



Ispizua L, et al. Drugs Today. 2003;39:453-68.

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## Pharmacological activity

- Selective blockade of peripheral histamine H<sub>1</sub> receptors
- PAF receptor antagonist
- Anti-inflammatory properties

Picolo C. Expert Opin Pharmacother. 2006; 7: 1989-2001.  
Keam SS. Drugs. 2007; 67:457-74.  
Muller J. Allergy. 2015; 70 (Suppl. 100): 1-14  
Bouquet L, et al. Allergy. 2006;61(Suppl 8):S-160.

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## Additional anti-inflammatory properties

- Inhibition of mast cell degranulation
- Inhibition of eosinophil and neutrophil chemotaxis
- Inhibition of cytokine production
- Inhibition of adhesion molecule expression
- Inhibition of transcription factors

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### Summary

- Potent, selective H<sub>1</sub>-receptor antagonist
- Antagonism of PAF receptors
- Inhibits several other mediators in the early and late phase inflammatory response
- Better symptomatic relief in allergic rhinitis and urticaria
- Proven efficacy and safety, in children aged between 2-11 years

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### Allergic Rhinitis: Clinical Efficacy of Rupatadine

- ▶ Rapid Onset of Action: Rhinitis
- ▶ Seasonal Allergic Rhinitis (SAR)
- ▶ Persistent Allergic Rhinitis (PER)
- ▶ Meta-Analysis of Rupatadine in Allergic Rhinitis
- ▶ Quality of Life (QoL)

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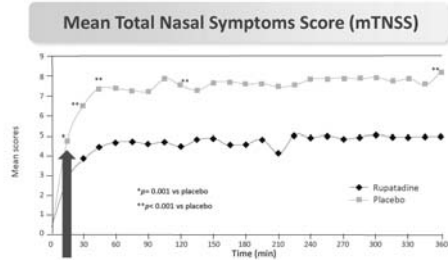
### Objective study measurements: Rapid onset of action and nasal obstruction

Treatment	Number of patients	Duration	Study design and level of evidence	Reference
PLA RUP 10 mg od	45	8 days	r, db, co Level 2	Stuebner P. Ann Allergy Asthma Immunol 2006;96:37-44.
PLA RUP 10 mg od	30	3 days	r, db, co Level 2	Valero A. JIACI 2009; 19 (6): 488-493.

Abbreviations: PLA=placebo, RUP=rupatadine, od=once daily, r=randomised, db=double-blind, co=crossover.

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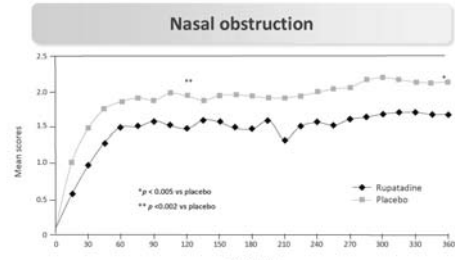
### Rupatadine vs placebo in the Vienna Challenge Chamber: Rapid onset of action



Stuebner P, et al. Ann of Allergy Asthma Immunol. 2006;96:37-44.

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### Rupatadine vs placebo in the Vienna Challenge Chamber: Nasal obstruction



Stuebner P, et al. Ann of Allergy Asthma Immunol. 2006;96:37-44.

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### SAR: Comparative studies

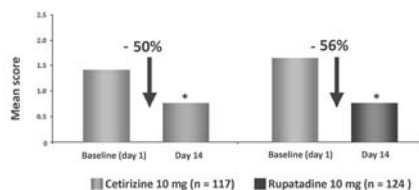
Treatment	Number of patients	Duration	Study design and level of evidence	Reference
RUP 10 mg od CTZ 10 mg od	124 117	2 weeks	m, r, db, pg Level 2	Martinez-Cocera C. JACI 2009; 133: 22-9.
PLA od RUP 10 mg od EBA 10 mg od	81 79 83	2 weeks	m, r, db, pg Level 2	Guadaño EM. Allergy 2004; 59: 766-71.
RUP 10 mg od RUP 20 mg od LOR 10 mg od	112 111 116	2 weeks	m, r, db, pg. Level 2	Saint-Martin F. JACI 2004; 14: 34-40.
RUP 10 mg od RUP 20 mg od LOR 10 mg od	107 112 112	2 weeks	m, r, db, pg Level 2	Inspeardo I. Drugs Today 2003; 39:451-468.
PLA od RUP 10 mg od DES 5 mg od	122 119 118	4 weeks	m, r, db, pg Level 2	Lukat KF. J Asthma Allergy 2013;5: 11-9
RUP 10 mg od LEV 10 mg od	30 30	2 weeks	sc, r, ol, pg Level 2	Matti R. Arch Otolaryngol Head Neck Surg 2010; 136: 796-800.

Abbreviations: CTZ=cetirizine, DES=desloratadine, EBA=ebastine, LEV=levocetirizine, LOR=loratadine, PLA=placebo, RUP=rupatadine, od=once daily, nm=non-medications, r=randomized, db=double-blind, od=open label, pg=parallel groups, sc=structured control.

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### SAR: Comparative studies vs cetirizine

#### Daily Total Symptom Score



\*p < 0.05 vs baseline

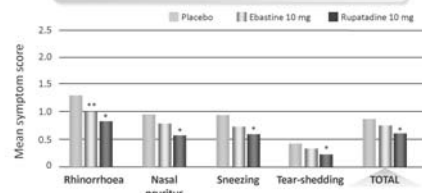
RUP 10 mg od	124	2 weeks	m, r, db, pg	Martinez-Cocera C. JACI 2009; 133: 22-9.
CTZ 10 mg od	117		Level 2	

Martinez-Cocera C. et al. Invest Allergol Clin Immunol. 2009;15:22-9.

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### SAR: Comparative studies vs ebastine

#### Mean daily symptom by symptom score



\* = p < 0.05 Rupatadine 10 mg vs placebo

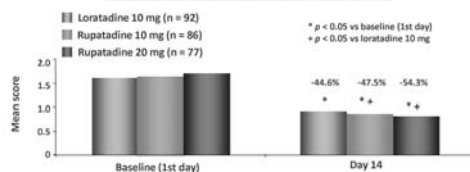
\*\* = p < 0.05 Ebastine 10 mg vs placebo

Guadaño EM. et al. Allergy. 2004;59:766-71.

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### SAR: Comparative studies vs loratadine

#### Total Daily Symptom Score



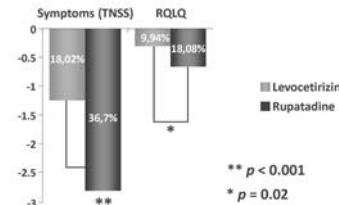
Saint-Martin F. et al. Invest Allergol Clin Immunol. 2004;14:34-40.

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### SAR: Comparative studies vs levocetirizine (l)

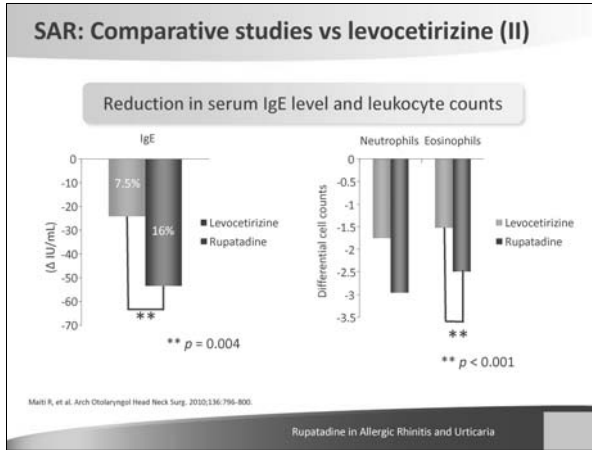
#### Nasal symptom reduction and quality of life

#### Mean difference vs first visit



Matti R. et al. Arch Otolaryngol Head Neck Surg. 2010;136:796-800.

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### Conclusions: SAR comparative studies

- **At least as effective as cetirizine, ebastine, loratadine and desloratadine in SAR patients**
- **Better safety and efficacy profile than levocetirizine**

Saint-Martin F. J Invest Allergol Clin Immunol. 2004; 14:34-40.  
Martinez-Cocera C, et al. J Invest Allergol Clin Immunol. 2005;15:22-9.  
Goulielmos EM, et al. Allergy. 2004; 59:766-71.  
Muller R. Allergy. 2015; 70 (Suppl. 100):S-14.  
Matti R. Arch Otolaryngol Head Neck Surg. 2010;136:796-800.  
Lukat KT, et al. J Asthma Allergy. 2013;6:29-9.

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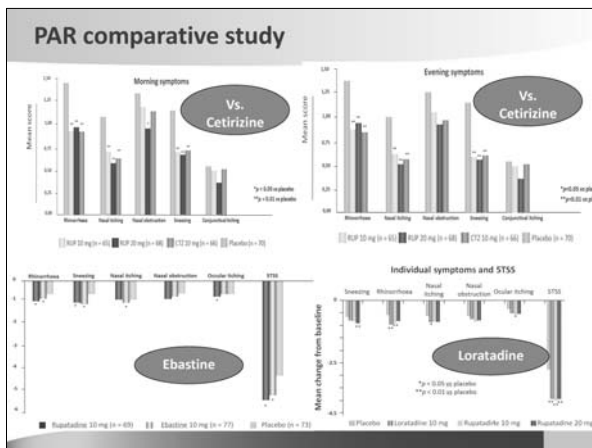
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### Studies in PAR

Treatment	Total number of patients	Duration	Study design and level of evidence	Reference
PLA RUP 10 mg od RUP 20 mg od	245	4 weeks	m, r, db, pc Level 2	Izquierdo I Drugs of Today 2003; 39: 451-468.
PLA RUP 10 mg od RUP 20 mg od CTZ 10 mg	70 65 68 66	4 weeks	m, r, db, pc Level 2	Marmouza F. J. Asthma and Allergy 2011; 4: 27-35.
PLA RUP 10 mg od EBA 10 mg od	73 71 79	4 weeks	m, r, db, pc Level 2	Molina M. Therapy 2010; 7(4): 426-429.
PLA RUP 10 mg od RUP 20 mg od LOR 10 mg od	69 73 71 70	4 weeks	m, r, db, pc Level 2	Kowalski et al. Therapy 2009; 6(3): 417-425.

Abbreviations: CTZ = cetirizine, PLA = placebo, RUP = rupatadine, od = once daily, m = multicentre, o = open, r = randomised, db = double-blind, pc = placebo-controlled.

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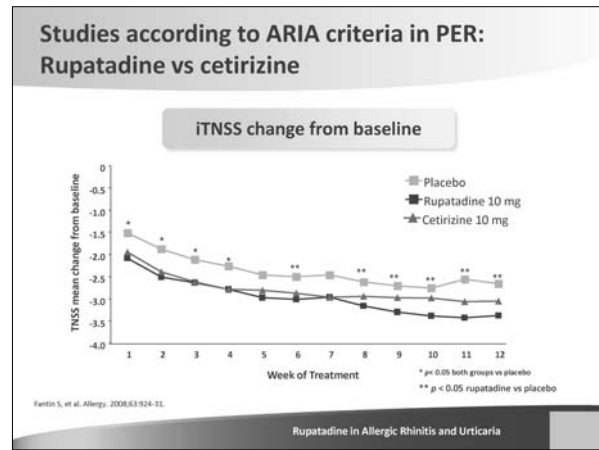
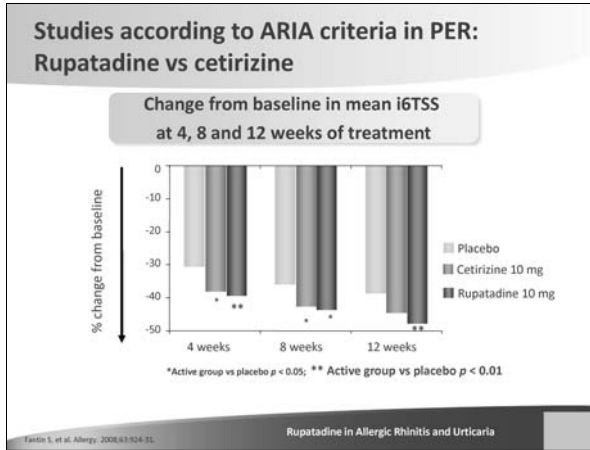


### Studies according to ARIA criteria in PER

Treatment	Number of patients	Duration	Study design and level of evidence	Reference
PLA RUP 10 mg od CTZ 10 mg od	185 183 175	12 weeks	m, r, db, pc Level 2	Fantini S. Allergy 2008; 63:924-31.
PLA RUP 10 mg od	324 in the 6-month study 120 in the 1-year study	12 months	m, o for 1 year	Valero A. Drug Safety 2009; 32(1):33-42.

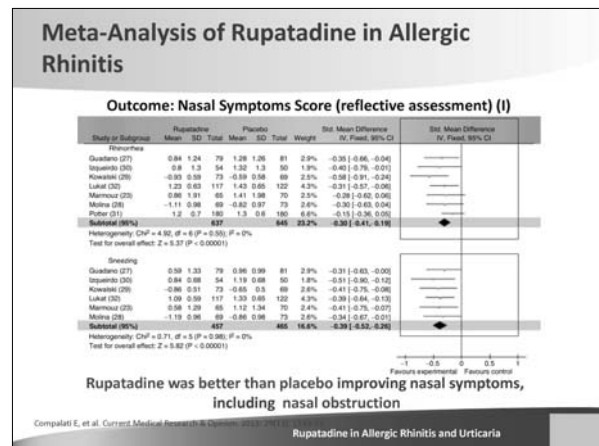
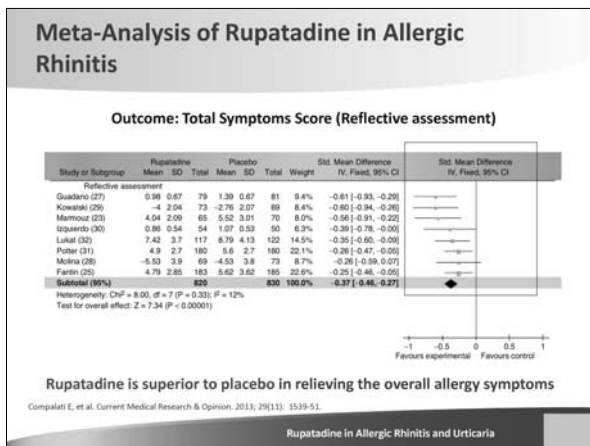
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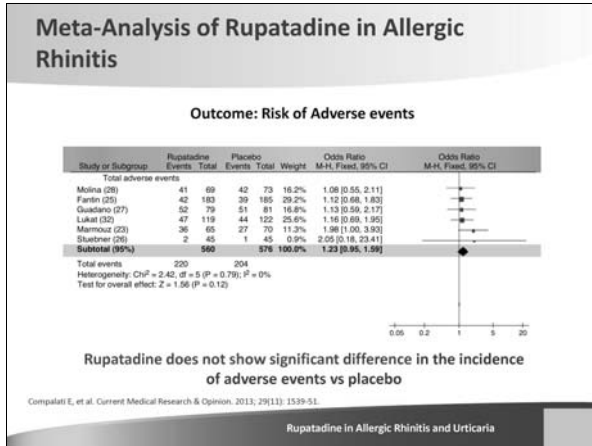
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- ### Meta-Analysis of Rupatadine in Allergic Rhinitis
- 387 articles out of 413 identified were screened and 17 were assessed using the full text (~Jan 2013)
  - 10 trials satisfied inclusion criteria and were suitable for quantitative analysis
- Compalati E, et al. Current Medical Research & Opinion. 2013; 1-13. Rupatadine in Allergic Rhinitis and Urticaria

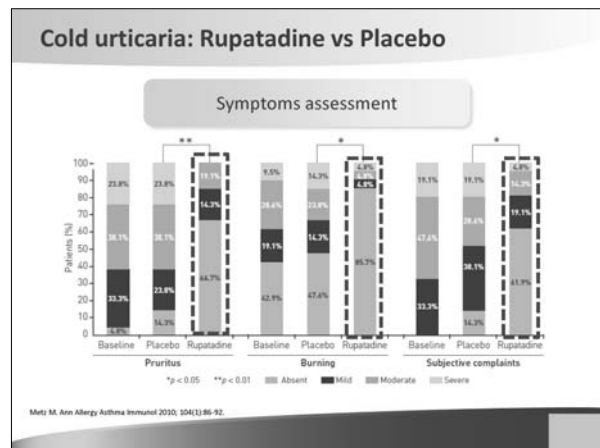
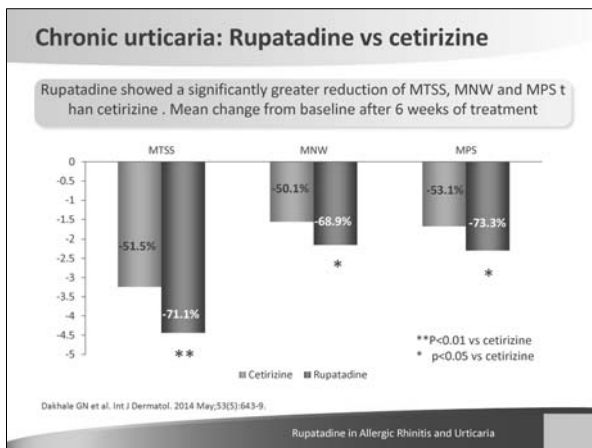
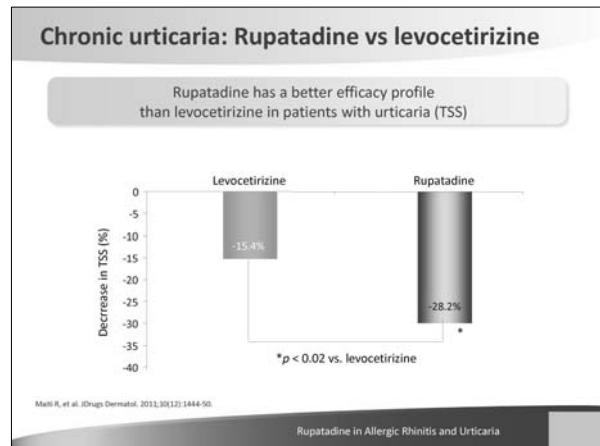


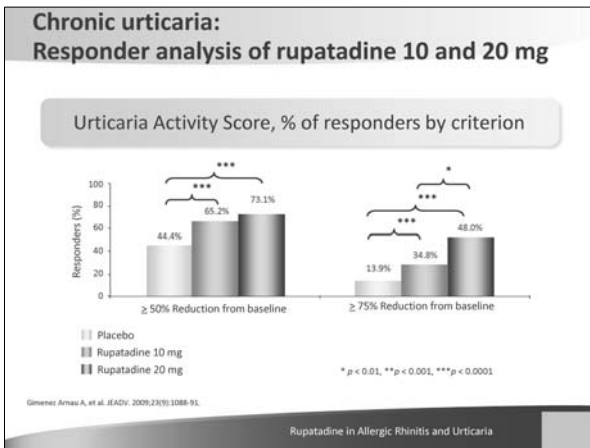
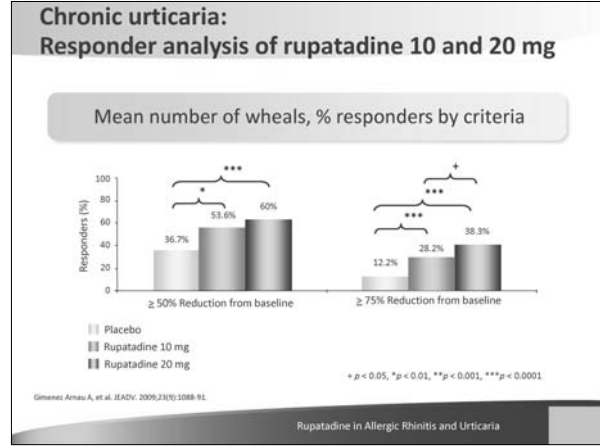
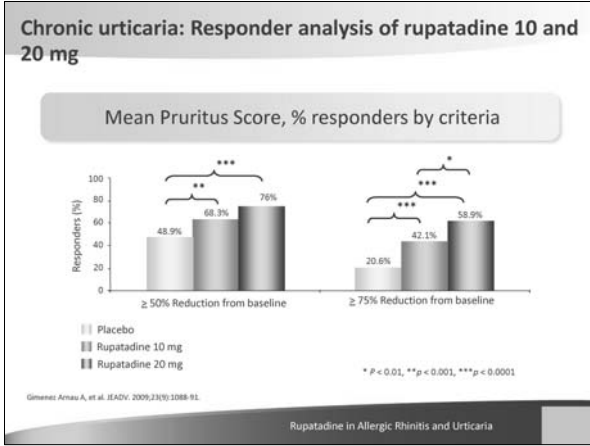


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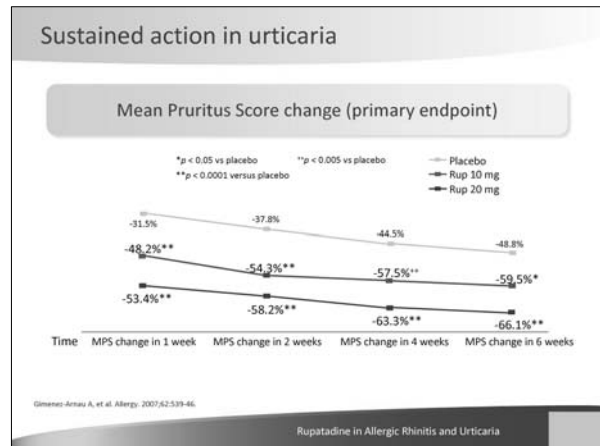
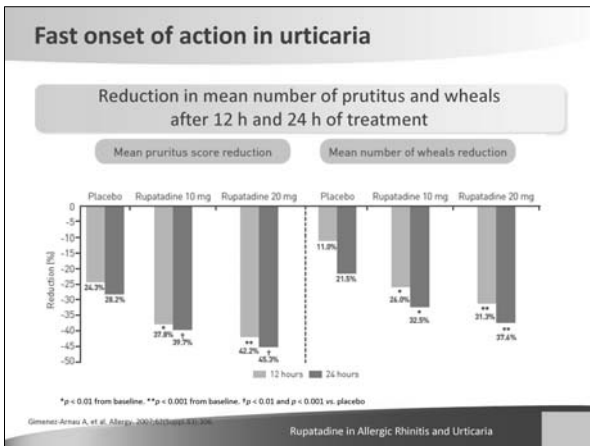
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- ▶ Efficacy in All Types of Urticaria
  - ▶ Fast Onset and Sustained Action in Urticaria
  - ▶ Quality of Life (QoL)
- Rupertadine in Allergic Rhinitis and Urticaria





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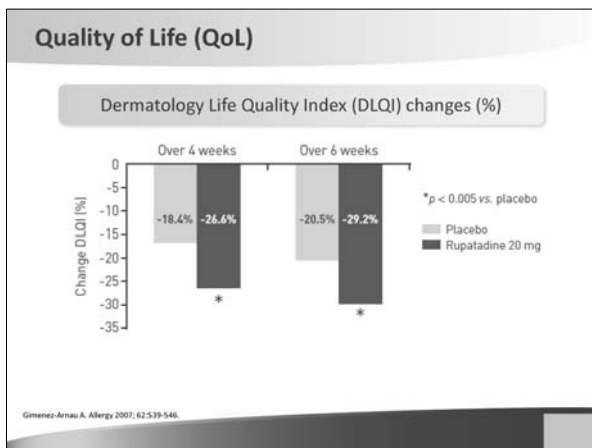
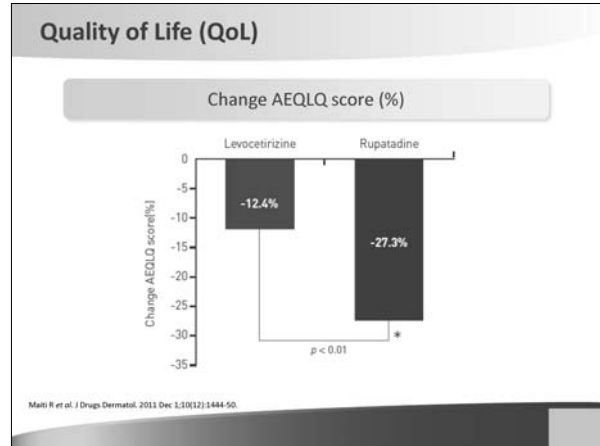




### Urticaria: Clinical Efficacy of Rupatadine

- ▶ Efficacy in All Types of Urticaria
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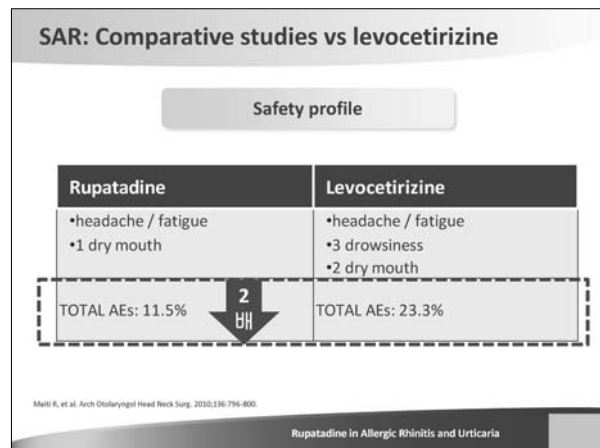
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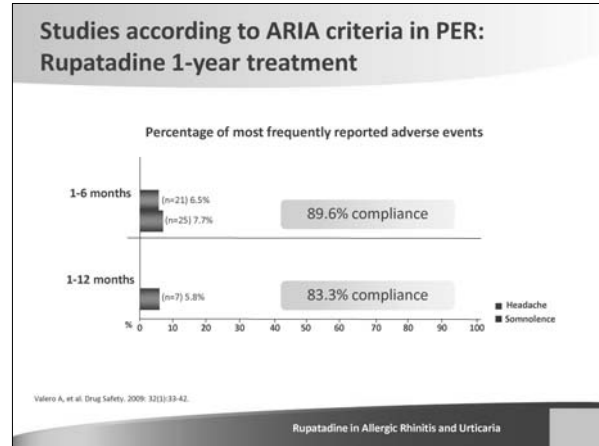
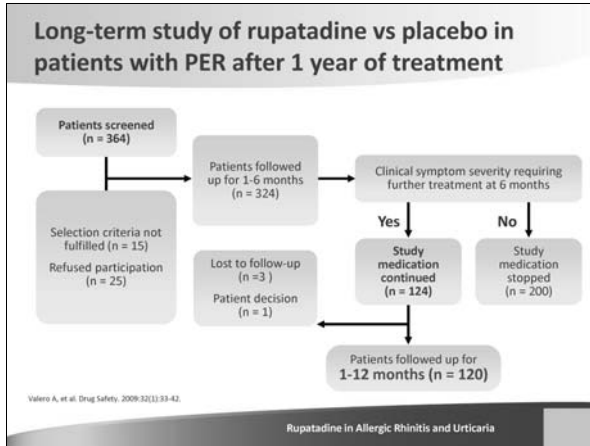
### Adverse Effects in Clinical Trials

Adverse event	Rupatadine (n = 2,025)	Placebo (n = 1,315)
Somnolence	9.5%	3.4%
Headache	6.9%	5.6%
Fatigue	3.2%	2.0%
Asthenia	1.5%	0%
Dry mouth	1.2%	0%
Dizziness	1.0%	0%

Pisano C. Expert Opin Pharmacother. 2006;7:1989-2001.  
Keem SE. Prescriber GL Drugs. 2007;67:407-74.  
SPC Rupatadine (Summary of Product Characteristics). May 2014.

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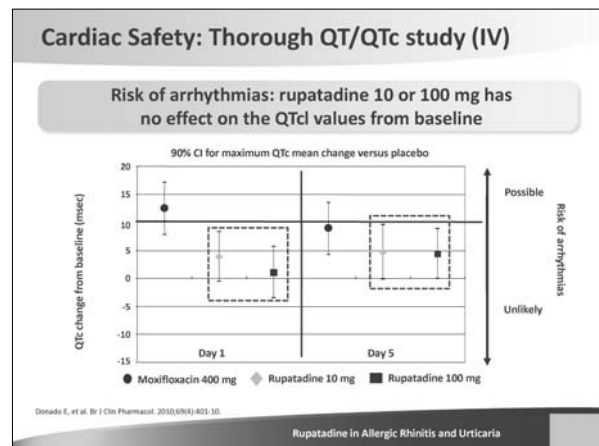
### CNS Effects in clinical studies

- Anticholinergic effects
  - Rupatadine does not have anticholinergic effects
    - ▶ No significant decrease in rupatadine 10-80 mg
- CNS depressant effects
  - At therapeutic doses, not produce CNS depressant effects

Barbanoj M, et al. Neuropsychobiology. 2004;50:111-21.

Barbanoj M, Hum Psychopharmacol Clin Exp. 2006;21:13-26.

Rupatadine in Allergic Rhinitis and Urticaria



### Convenience of treatment: Administration with food and juice

- Food
  - ▶ No clinical relevance and rupatadine may be taken with or without food
- Grapefruit Juice
  - ▶ Taking rupatadine with grapefruit juice is not recommended

Picado C. Expert Opin Pharmacother. 2006;7:1989-2001.

Solano A, et al. Clin Therapeutics. 2007;29:900-8.

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### Drug-drug interactions

- Via microsomal pathways involving the CYP3A4 enzyme
- Avoid co-administration of rupatadine with ketoconazole and erythromycin
- Could be co-administered with azithromycin, fluoxetine or lorazepam
- With alcohol did not increase the cognitive and psychomotor impairment

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### Rupatadine: Conclusions

**Pharmacology**

- Dual Action; **Antihistamine + Anti-PAF**
- Broad Action; Inhibits several **other mediators**

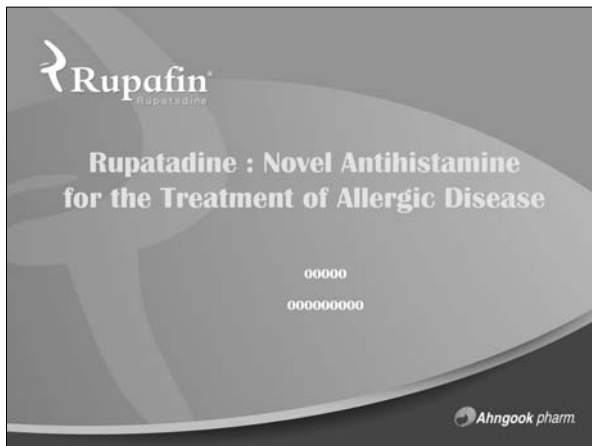
**Clinical efficacy: Allergic rhinitis**

- **Significantly reduced** the overall nasal symptoms
- **Improves patients' quality of life** and significantly **reduces AR severity**

**Safety profile**

- **No significant negative effects** on cognition or psychomotor activity
- **Long-term safety and compliance**

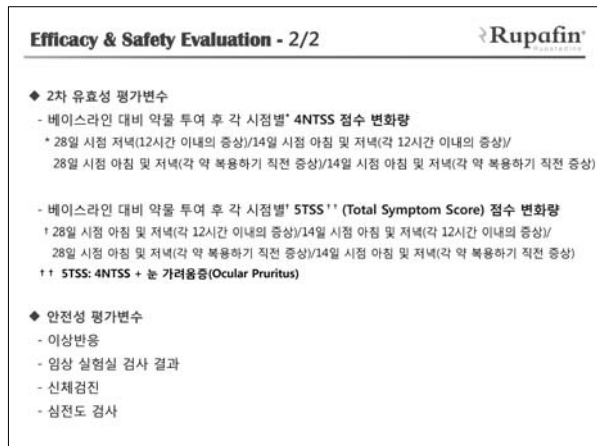
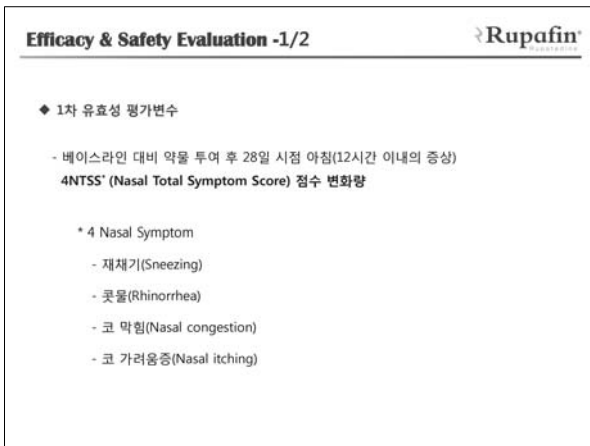
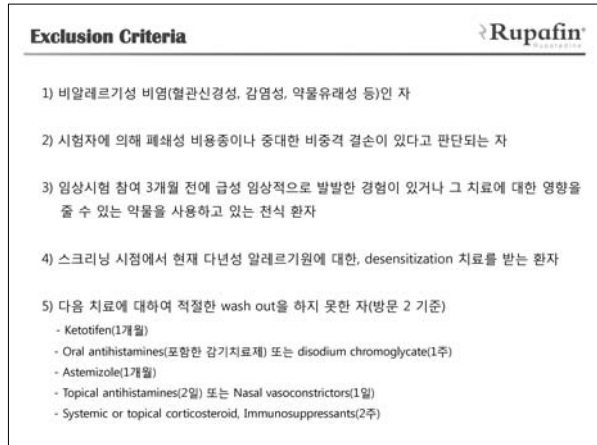
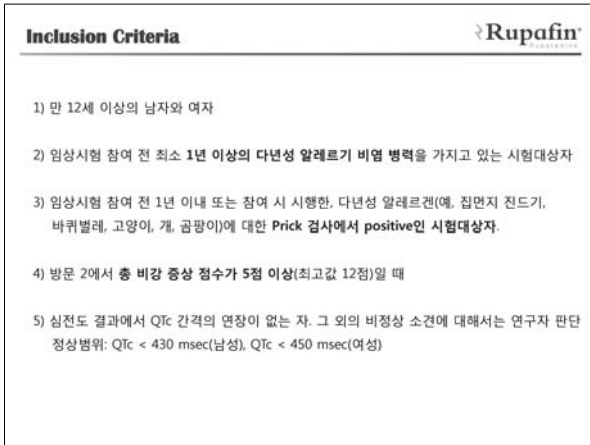
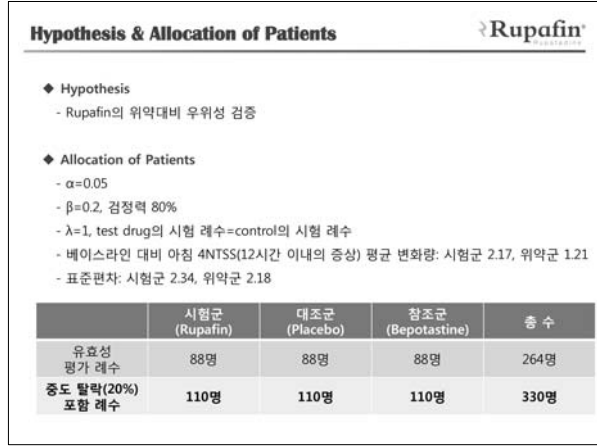
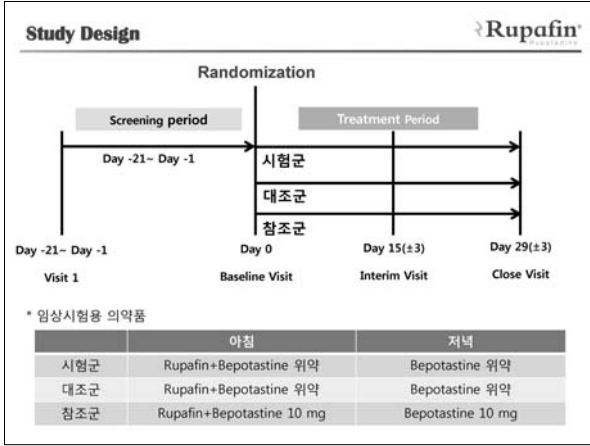
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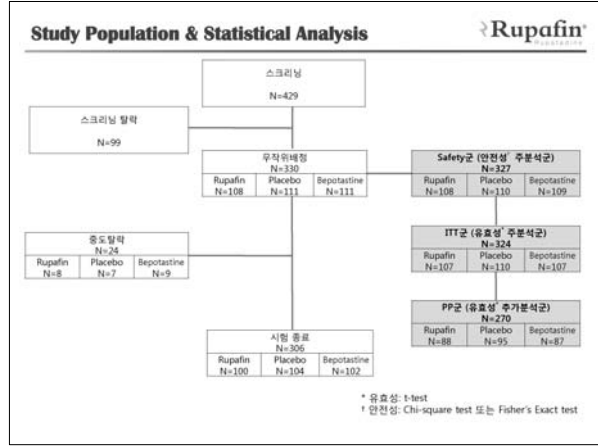


### Study Objective

Rupafin

- ◆ **Title of the Study**  
한국인 다년성 알레르기 비염 환자를 대상으로 AGR정의 유효성 안전성 평가를 위한 4주, 다기관, 이중눈가림, 무작위배정, 위약 대조군, 제 3상 가교 임상시험
- ◆ **Primary Endpoint**  
한국인 다년성 알레르기 비염 환자에게 위약 대비 Rupafin<sub>8</sub>(루파타딘 푸마르산염)의 안전성과 유효성 평가
- ◆ **Secondary Endpoint**  
Caucasian에게 실시한 임상시험의 안전성과 유효성 자료를 바탕으로 한국인에 대한 안전성과 유효성 자료를 확보하기 위한 가교시험





### Baseline Characteristics

◆ 성별/연령/다년성 알레르기성 비염 유병기간

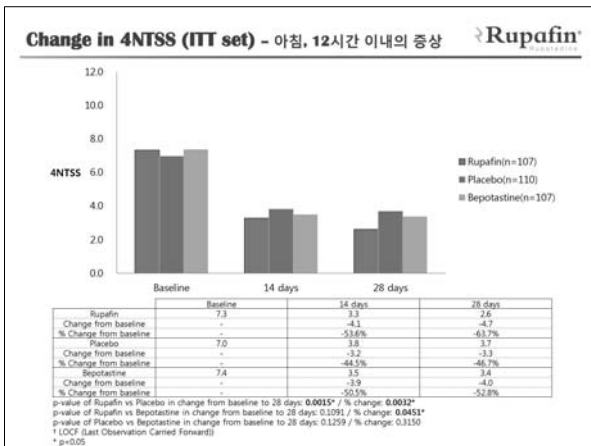
	Rupafin (N=108) n(%)	Placebo (N=110) n(%)	Bepotastine (N=109) n(%)	합계 (N=327) n(%)	p-value
<b>성별</b>					
남성	50(46.30)	50(45.45)	47(43.12)	147(44.95)	0.8878
여성	58(53.70)	60(54.55)	62(56.88)	180(55.05)	
합계	108(33.03)	110(33.64)	109(33.33)	327(100.00)	CHI-square test
<b>연령</b>					
mean ± std (세)	28.63 ± 10.00	28.14 ± 9.20	30.68 ± 9.09	29.15 ± 9.47	0.1091
median	26.00	26.00	29.00	26.00	ANOVA
min - max	15.00 - 65.00	12.00 - 56.00	15.00 - 60.00	12.00 - 65.00	
<b>유병기간</b>					
n(%)	27(34.18)	22(27.85)	30(37.97)	79(100.00)	0.4480
mean ± std (개월)	81.93 ± 63.87	93.68 ± 82.00	70.03 ± 55.12	80.68 ± 66.27	ANOVA
median	65.00	73.50	43.50	63.00	
min - max	14.00 - 245.00	12.00 - 367.00	12.00 - 217.00	12.00 - 367.00	

### Change in 4NTSS (ITT set)

□ Primary Endpoint

			Rupafin (n=107)	Placebo (n=110)	Bepotastine (n=107)	p-value*	p-value†	p-value*
아침, 12시간 이내의 증상	Change from baseline to 14 days	mean ± std	-4.07 ± 3.09	-3.16 ± 3.01	-3.88 ± 3.17	0.0304*	0.6626	0.8895
	Change from baseline to 28 days	mean ± std	-4.74 ± 3.24	-3.28 ± 3.42	-4.00 ± 3.47	0.0015*	0.1091	0.1259
아침, 약 복용 직전 증상	Change from baseline to 14 days	mean ± std	-4.02 ± 3.10	-3.36 ± 3.10	-3.92 ± 3.04	0.1207	0.8068	0.1868
	Change from baseline to 28 days	mean ± std	-4.72 ± 3.13	-3.51 ± 3.51	-4.07 ± 3.40	0.0080*	0.1450	0.2369
저녁, 12시간 이내의 증상	Change from baseline to 14 days	mean ± std	-4.23 ± 2.89	-3.14 ± 3.00	-3.96 ± 3.14	0.0067*	0.5122	0.0496*
	Change from baseline to 28 days	mean ± std	-4.56 ± 3.26	-3.27 ± 3.37	-4.13 ± 3.61	0.0046*	0.3619	0.0703
저녁, 약 복용 직전 증상	Change from baseline to 14 days	mean ± std	-4.32 ± 2.91	-3.49 ± 3.06	-4.20 ± 3.07	0.0435*	0.7666	0.0925
	Change from baseline to 28 days	mean ± std	-4.63 ± 3.19	-3.56 ± 3.38	-4.20 ± 3.54	0.0178*	0.3519	0.1758

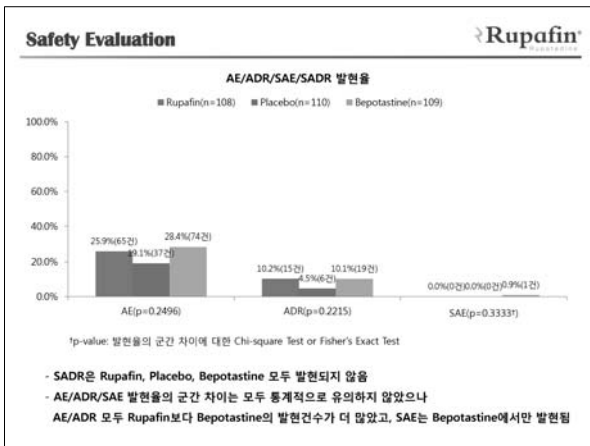
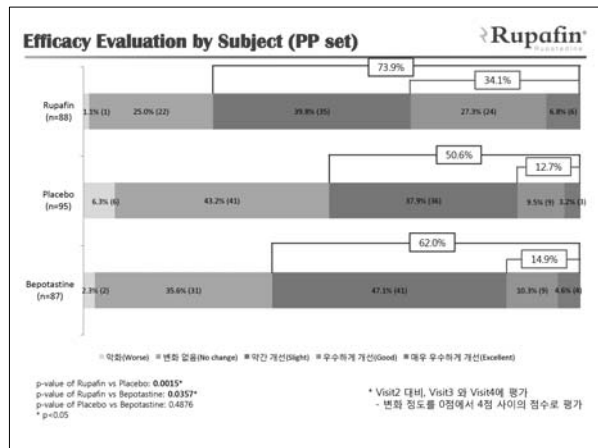
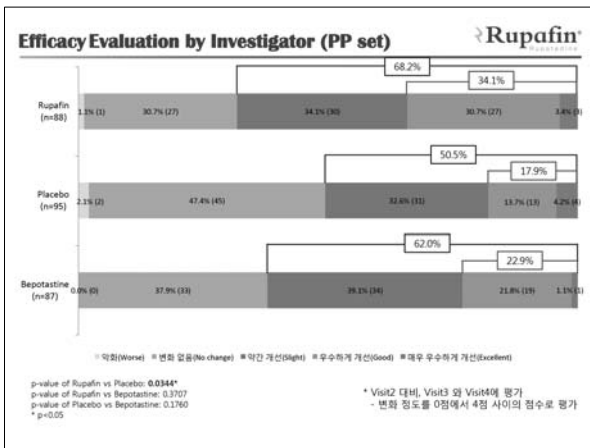
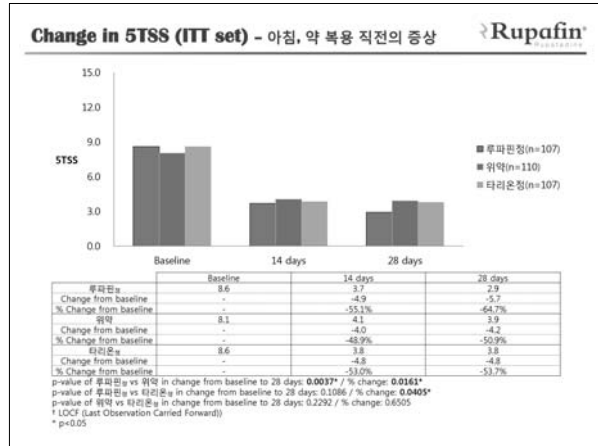
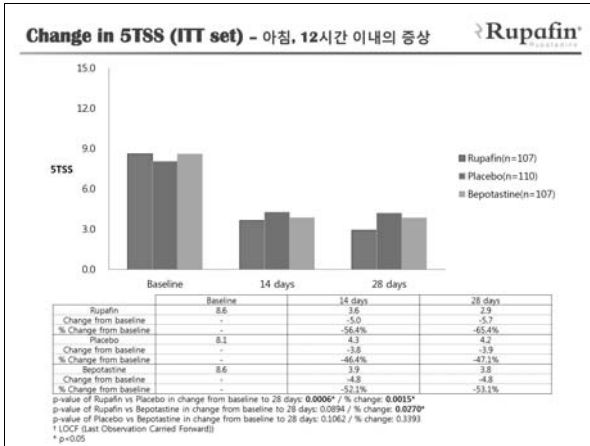
p-value\* t-test for Rupafin vs Placebo  
p-value† t-test for Rupafin vs Bepotastine  
p-value\* t-test for Placebo vs Bepotastine  
\* p<0.05



### Change in 5TSS (ITT set)

			Rupafin (n=107)	Placebo (n=110)	Bepotastine (n=107)	p-value*	p-value†	p-value*
아침, 12시간 이내의 증상	Change from baseline to 14 days	mean ± std	-4.96 ± 3.48	-3.78 ± 3.41	-4.75 ± 3.79	0.0124*	0.6661	0.0496*
	Change from baseline to 28 days	mean ± std	-5.69 ± 3.67	-3.85 ± 4.04	-4.77 ± 4.24	0.0006*	0.0894	0.1062
아침, 약 복용 직전 증상	Change from baseline to 14 days	mean ± std	-4.92 ± 3.51	-4.00 ± 3.51	-4.77 ± 3.62	0.0561	0.7593	0.1148
	Change from baseline to 28 days	mean ± std	-5.68 ± 3.60	-4.15 ± 4.08	-4.82 ± 4.19	0.0037*	0.1086	0.2292
저녁, 12시간 이내의 증상	Change from baseline to 14 days	mean ± std	-5.17 ± 3.27	-3.80 ± 3.43	-4.84 ± 3.80	0.0030*	0.5006	0.0355*
	Change from baseline to 28 days	mean ± std	-5.49 ± 3.70	-3.84 ± 3.97	-4.91 ± 4.34	0.0019*	0.2941	0.0617
저녁, 약 복용 직전 증상	Change from baseline to 14 days	mean ± std	-5.22 ± 3.25	-4.13 ± 3.43	-5.07 ± 3.69	0.0173*	0.7535	0.0532
	Change from baseline to 28 days	mean ± std	-5.57 ± 3.63	-4.15 ± 3.91	-5.03 ± 4.30	0.0063*	0.3205	0.1179

p-value\* t-test for Rupafin vs Placebo  
p-value† t-test for Rupafin vs Bepotastine  
p-value\* t-test for Placebo vs Bepotastine  
\* p<0.05



### Adverse Drug Reaction

#### ADR의 주요 PT (Preferred Term) 발현율

발현율	Rupafin (n=108)		Placebo (n=110)		Bepotastine (n=109)	
	발현율 (%)	발현건수	발현율 (%)	발현건수	발현율 (%)	발현건수
Headache	21.85	2	10.91	1	21.83	2
Somnolence	76.48	7	10.91	1	63.47	4
Dizziness	00.00	0	10.91	1	00.00	0
Narcolepsy	10.91	1	00.00	0	00.00	0
Nasopharyngitis	00.00	0	00.00	0	10.92	1
Dyspepsia	00.00	0	00.00	0	10.92	1
Abdominal pain	00.00	0	00.00	0	10.92	1
Constipation	00.00	0	00.00	0	10.92	1
Nausea	00.00	0	00.00	0	10.92	1
Nasal dryness	10.91	1	00.00	0	10.92	1
Alanine aminotransferase increased	10.91	1	10.91	1	10.92	1
Aspartate aminotransferase increased	10.91	1	10.91	1	10.92	1
Gamma-glutamyltransferase increased	10.91	1	00.00	0	10.92	1
Blood bilirubin increased	00.00	0	10.91	1	00.00	0
Platelet count increased	00.00	0	00.00	0	10.92	1
Dry eye	00.00	0	00.00	0	10.92	1
Asthenia	00.00	0	00.00	0	10.92	1
Thirst	00.00	0	00.00	0	10.92	1
Urinary	10.91	1	00.00	0	00.00	0
<b>Total</b>	<b>11(10.19)</b>	<b>15</b>	<b>5(4.55)</b>	<b>6</b>	<b>11(10.09)</b>	<b>19</b>



Study Conclusion

**Rupafin®**  
RUPATADINE

**Conclusion**

- ◆ 유효성
  1. 투여 28일 후 4NTSS 점수 변화량을 비교한 결과, ITT 분석군 및 PP 분석군 모두에서 Rupafin이 Placebo에 비하여 우위성을 만족함
  2. 투여 28일 후 4NTSS 점수 변화율을 비교한 결과,
    - 1) ITT 분석군 및 PP 분석군 모두에서 Rupafin이 Placebo에 비하여 우위성을 만족함
    - 2) ITT 분석군에서 Rupafin이 Bepotastine에 비하여 우위성을 만족함

→ Rupafin은 위약 및 Bepotastine에 비하여 투여 28일 후 4NTSS 점수 변화량 및 변화율 모두에서 우위성을 만족함
- ◆ 안전성
  1. AE/ADR/SAE 발현율을 비교한 결과, Rupafin, Placebo 및 Bepotastine의 중간 차이는 통계적으로 유의하지 않았음(SADR은 세 군 모두 0%)
  2. Rupafin은 Bepotastine에 비하여 AE/ADR 발현건수가 더 낮았음

**Product Information** **Rupafin®**  
RUPATADINE

루파핀® 정 / Rupafin® tab.	
제품분류	전문의약품 / 항히스타민제 (2세대)
성분/함량	Rupatadine fumarate 12.8mg (10.0mg as rupatadine)
허가일자	2017년 4월 28일
발매일자	2017년 12월 1일 (TBD)
약가	TBD
규격/포장단위	10T, 30T, 100T (PTP)
효능효과	알레르기 비염, 두드러기 증상 치료 (소양증, 발적 등)
용법용량	12세 이상 - 1일 1회, 1회 1정
원개발사	Uriach Pharma / Spain
비고	2001년 스페인 최초 허가 및 2003년 발매 / 70여개국에서 판매중

