Name of Sponsor/Company: Astellas Pharma Korea, Inc.		
Name of Finished Product: Prograf®		
Name of Active Ingredient: Tacrolimus		

SYNOPSIS

Title of Study: Open-Label, Randomized, Comparative, Multi-Center Clinical Trial on the Therapeutic Effect of Tacrolimus (Prograf Cap.®) in Combination with Low-Dose Corticosteroid Compared or High-Dose Corticosteroid alone in Patients with Minimal-Change Nephrotic Syndrome (MCNS)

Investigators/Coordinating Investigator:

Investigational Site	Department	Name
[redacted]	[redacted]	[redacted]

Study Center(s):

A total of 15 study sites

Publication Based on the Study:

Not applicable

Study Period

Study Initiation Date (Date of First Enrollment):

16 Jul 2012

Study Completion Date (Date of Last Evaluation):

21 Aug 2017

Phase of Development:

Phase 3

Objectives: To compare the therapeutic effect of tacrolimus (Prograf Cap.) in combination with low-dose corticosteroid or high-dose corticosteroid alone in patients with minimal-change nephrotic syndrome.

Methodology:

This study was a Phase 3, multicenter, randomized (1:1), open, parallel group, non-inferiority study comparing 2 groups treated with 0.5 mg/kg once a day steroid in combination with 0.05 mg/kg twice a day tacrolimus in the test group and 1 mg/kg once a day steroid in the control group for 24 weeks, which included the remission and tapering/maintenance phases.

This study consisted of 2 phases, Remission and Tapering & Maintenance.

Remission phase: The period until UPCR<0.2 is reached after the start of the treatment (up to 8 weeks). 0.5 mg/kg steroid was administered in combination with tacrolimus 0.05 mg/kg/day in the test group, and 1 mg/kg steroid only in the control group. As for the test group, the tacrolimus trough concentration in the blood was maintained at 5-10 ng/ml.

Tapering and maintenance phase: The period from the remission phase up to 24 weeks. After the complete remission induction, 0.5 mg/kg steroid in combination with tacrolimus 0.05 mg/kg/day was administered in the test group, and 1 mg/kg steroid in the control group, for 2 weeks. After that, the dose of the steroid was decreased by 5 mg every week in both groups, and the tacrolimus trough concentration was maintained at 3-8 ng/ml. The subjects were instructed by the study coordinator regarding the schedule for decreasing the steroid dose at the outpatient visits and through weekly phone calls.

Number of Patients (Planned, Enrolled and Analyzed):

Planned: 152 (considering a withdrawal rate of 15%; 76 subjects per group)

Actual: Safety Set:136 subjects, ITT: 136 subjects, PP: 83 subjects for the primary efficacy assessment and 77 subjects for the secondary efficacy assessment.

	Test Group	Control Group	Total
Randomized	69	75	144
Intention to treat set	67	69	136
Safety Set	67	69	136
Per Protocol Set for the primary efficacy assessment	39	44	83
Per Protocol Set for the secondary efficacy assessment	36	41	77

Source: Table 6.1.2

Diagnosis and Main Criteria for Inclusion:

1) Male or female patients who are 16 years old or more and less than 80 years old;
2) Patients who have been diagnosed with initial or relapsed primary MCNS;
3) Patients whose UPCR is 3.0 or more at visit 1 (spot urine); and
4) Patients who voluntarily consented to participate in the study by signing the informed-consent form (patients who are19 or older can sign the informed-consent form by themselves; for 16- to 18-year-old patients, they and their parents have to sign the consent forms).

Test Product, Dose and Mode of Administration, Batch Numbers:

1) Test Product: Tacrolimus (Prograf Cap)

2) Dose and Mode of Administration: For the test group, 0.05 mg/kg bid tacrolimus was administered till 2 weeks for after complete remission with the tacrolimus trough level at 5-10 ng/ml and then was maintained at 3-8ng/ml up to 24 weeks or relapse.
3) Batch Numbers:
   - Tacrolimus (Prograf) 0,5mg: [redacted]
   - Tacrolimus (Prograf) 1.0mg: [redacted]

Duration of Treatment (or Duration of Study, if applicable):

24weeks

Reference Product, Dose and Mode of Administration, Batch Numbers:

1) Test Product: Prednisolone (Solondo Tab.®)
2) Dose and Mode of Administration: 0.5mg/kg and 1mg/kg steroid were administered in the test group and the control group, respectively till 2 weeks after the remission phase. After that, the dose of the steroid was decreased by [redacted]y week in both groups up to 24 weeks or relapse.
3) Batch Numbers: [redacted]

Criteria for Evaluation:

1) Primary efficacy endpoint

   The percentage of subjects who show a decreased UPCR of less than 0.2 up to 8 weeks
2) Secondary efficacy endpoints
   - The period until the UPCR has decreased to below 0.2
   - The percentage of subjects who show relapse after remission up to 24 weeks
   - The period until relapse happens from complete remission up to 24 weeks
3) Safety

   All AEs was assessed based on the symptoms that the subjects complained of the measured vital signs, the results of the physical examination to be conducted by the investigators, and the results of the electrocardiogram, chest X-ray, hematology, chemistry, and urinalysis. The percentage of AEs up to 24 weeks was evaluated after the administration of the investigational drug.

Statistical Methods:

1) Efficacy analysis

   The evaluation of the primary and secondary efficacy was conducted through a one-tailed test at a 2.5% significance level and a two-tailed test at a 5% significance level, respectively. The efficacy analysis was performed mainly in the intention-to-treat (IIT) and additionally per protocol (PP) groups.

   - <u>The primary efficacy endpoint</u>

     The complete remission rates of the control and test groups were defined as δ, a one-tailed test was performed using a 95% lateral confidence level upper limit of δ at a 2.5% significance level. If the 95% lateral confidence level upper limit is less than 0.2, it means that the effect of the test drug is inferior to that of the control drug. If it is 0.2 or more, it means that the test drug is not inferior to the test drug.

   - <u>Secondary efficacy endpoint</u>

     -The period until the UPCR decreases to below 0.2 in both the test and control groups: The median time was presented, and the log rank test was carried out to compare the test and control drugs.

     -The percentage of subjects who show relapse after remission up to 24 weeks in both the test and control groups: Chi-square test or Fisher's exact test was carried out to obtain this value.

-The period until relapse occurs from complete remission up to 24 weeks in both the test and control groups: The median time was presented, and the log rank test was carried out to compare the test and control drugs.

2) Safety analysis

The percentage of AEs up to 24 weeks was evaluated after the administration of the investigational drug and compared by group via chi-square test or Fisher's exact test. As for the laboratory test results, results of the continuous variables were compared to those of visit 1(screening visit) in both groups. The changes in value were analyzed using t-test and Wilcoxon rank sum test. The frequency and percentage on each visit were described for results of categorical variables. As for the values of the vital signs and the other biological test results were compared to those of visit 1(screening visit) in both groups. The changes in value were analyzed using t-test and Wilcoxon rank sum test.

Summary of Results/Conclusions:

Subject Disposition:

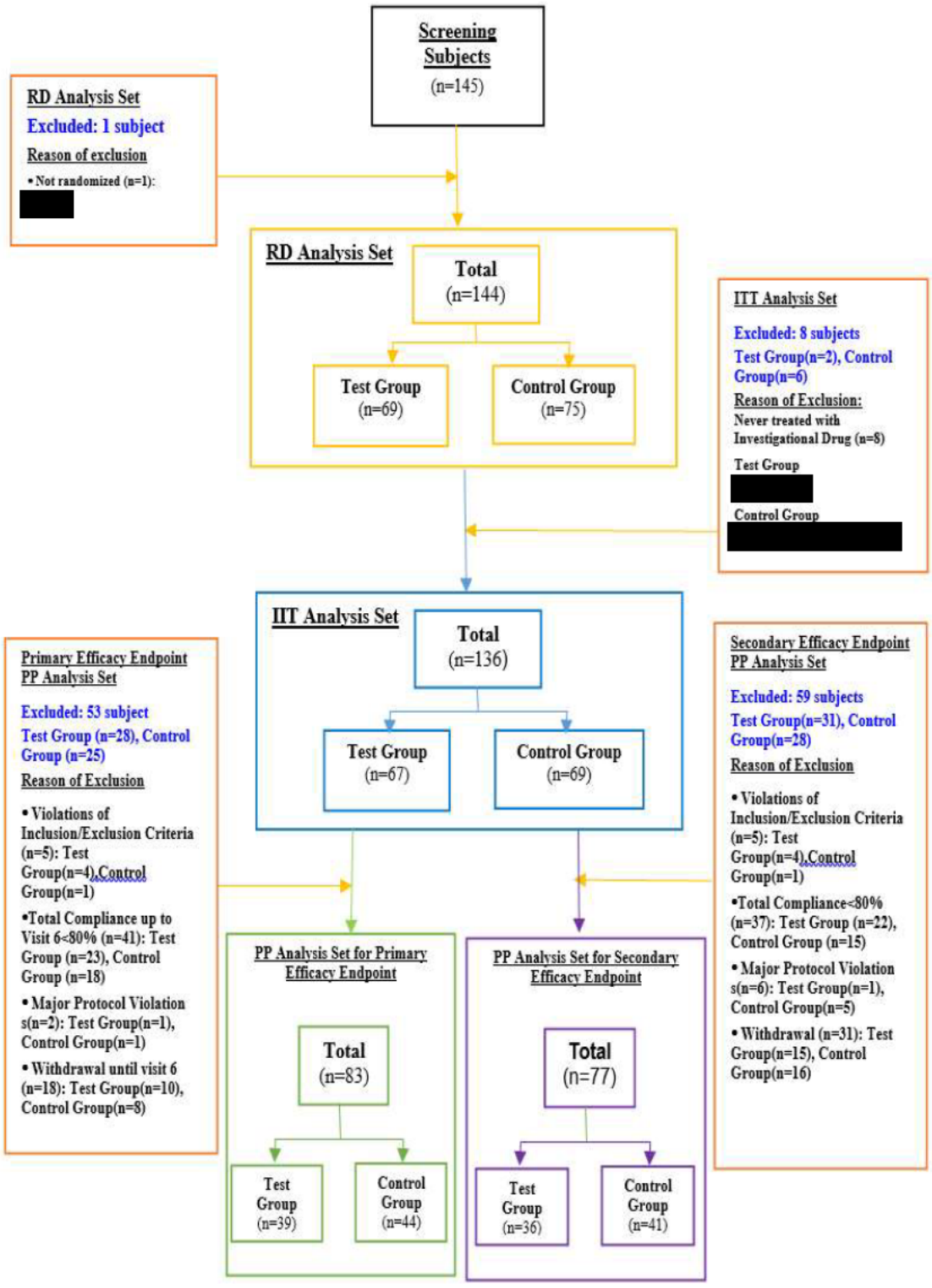
The study was conducted in 15 sites. For 145 subjects in total were screened, whether they were eligible for this study was confirmed. 144 subjects were enrolled, except 1 screening failures: 69 subjects were randomized into test group and 75 subjects were randomized into control group. 144 randomized subjects were included in the randomized (RD) analysis set excluding 1 Subject; 136 subjects (67 for the test group vs. 69 for the control group) who were given the test drug or control drug at least once after randomization were included in the ITT analysis set (8 subjects were not Treated (Investigational drug unused)). In the course of the study, 31 subjects were withdrawn in the ITT analysis set. The primary PP analysis set was defined as 83 subjects (39 vs. 44) who satisfied the inclusion/exclusion criteria, showed an overall compliance of 80% or more, and conducted and completed the study in compliance with the protocol. The secondary PP analysis set was defined as 77 subjects (36 vs 41) who satisfied the inclusion/exclusion criteria, showed an overall compliance of 80% or more, and conducted and completed the study in compliance with the protocol. The safety analysis set included 136 enrolled subjects (67 vs. 69) who were given the test drug or control drug at least once.

Table 1. Subject enrollment status

	Test Group	Control Group	Total
Eligibility for study enrollment, n	-	-	145
Not randomized	-	-	1
Randomized, n	69	75	144
Treated	67	69	136
Not Treated(Investigational drug unused)	2	6	8
Completed, n	54	59	113
Withdrawal, n	15	16	31
· Protocol violations other than inclusion/exclusion criteria violations	2	4	6
· Difficulty in study conduct due to adverse events	5	6	11
· Patient did not want to participate any more for reasons other than adverse events	6	5	11
· Subject did not comply with the instructions of principal investigator or investigator	1	0	1
· Investigator's judgment	1	1	2

Source: Table 6.1.2 and Appendix 13.2.1

Figure 1. Disposition of Subjects



Source: Table 6.1.2

Efficacy Results:

1) Primary Efficacy Endpoint

- Percentage of subjects who showed a decreased UPCR of less than 0.2 up to 8 weeks in both the test and control groups (8-week complete remission rate)

For the ITT analysis set, a difference in the 8-week complete remission rate between the control and test group was -2.29%; the upper confidence limit was 11.63%, smaller than the non-inferiority margin of 20%. This result suggests the test drug is not inferior to the control drug.

For the PP analysis set, a difference in the 8-week complete remission rate between the control and test group was 1.75%; the upper limit of the confidence interval was 16.95%, smaller than the non-inferiority margin of 20%. This result suggests the test drug is not inferior to the control drug.

It demonstrated non inferiority, leading to a final conclusion that the test drug is not inferior to the control drug.

Table 2. Percentage of subjects who showed a decreased UPCR of less than 0.2 up to 8-weeks in both the test and control groups (8-week complete remission rate)

	Test Group	Control Group	Total
ITT analysis set, n	**67**	**69**	**136**
Percentage of subjects who showed a decreased UPCR of less than 0.2 up to 8 weeks, n (%)	53(79.1)	53(76.81)	106(77.94)
Difference in a complete remission rate between control and test groups (control group - test group, %)		-2.29	
Confidence interval for a difference in a complete remission rate		[-∞, 11.63][1)]	
PP analysis set, n	**39**	**44**	**83**
Percentage of subjects who showed a decreased UPCR of less than 0.2 up to 8 weeks, n (%)	33 (84.62)	38 (86.36)	71 (85.54)
Difference in a complete remission rate between control and test groups (control group - test group, %)		1.75	
Confidence interval for a difference in a complete remission rate		[-∞, 16.95][1)]	

Source: Appendix 13.2.6 and Appendix 13.2.8.3
1) If the upper limit of the confidence interval was less than 20 %, it proved that the effect of the test drug is not inferior to that of the control drug.

2) **Secondary Efficacy Endpoint**

- Period until the UPCR was decreased to less than 0.2 in test and control groups

For the ITT analysis set, the median time was 15 days (95% C.I: 14-27) in the test group and 25 days (95% C.I: 14-28) in the control group. The log-rank test showed there was no significant difference between the groups (P-value=0.164).

For the PP analysis set, median time was 15.5 days (95% C.I: 14-27) in the test group and 15 days (95% C.I: 14-28) in the control group. The log-rank test showed there was no significant difference between the groups (P-value=0.789).

Table 3. Period until the UPCR was decreased to less than 0.2 in test and control groups

	Test Group	Control Group	Total	P-value
ITT analysis set, n	67	69	136	
Period until the UPCR was decreased to less than 0.2				
median time	15	25	16	0.164 1)
95% CI	[14,27]	[14,28]	[14,27]	
PP analysis set, n	36	41	77	
Period until the UPCR was decreased to less than 0.2				
median time	15.5	15	15	0.789 1)
95% CI	[14,27]	[14,28]	[14,26]	

Source: Appendix 13.2.6 and Appendix 13.2.8.3
1) P-value by Log-rank test

- Percentage of subjects who showed recurrence after complete remission up to 24 weeks

The total number of subjects who showed recurrence after complete remission up to 24 weeks was 15 (14.15%): 3 (5.66%) in the test group vs. 12 (22.64%) in the control group as the result of ITT analysis. The chi-square test showed there was a significant intergroup difference at a 5% significance level (P-value=0.012). For the PP analysis set, the total number of subjects who showed recurrence after complete remission up to 24 weeks was 9 (13.43%): 1 (3.23%) vs. 8 (13.43%). The chi-square test showed there was a significant intergroup difference at a 5% significance level (P-value=0.023).

Table 4. Percentage of subjects who showed recurrence after complete remission up to 24 weeks

	Test Group	Control Group	Total	P-value
ITT analysis set, n	67	69	136	
No. of subjects who showed complete remission until 8 weeks, n	53	53	106	
Percentage of subjects who showed recurrence after complete remission up to 24 weeks[1)]	3 (5.66)	12 (22.64)	15 (14.15)	0.012††
PP analysis set, n	36	41	77	
No. of subjects who showed complete remission until 8 weeks, n	31	36	67	
Percentage of subjects who showed recurrence after complete remission up to 24 weeks[1)]	1 (3.23)	8 (22.22)	9 (13.43)	0.023††

Source: Appendix 13.2.6 and Appendix 13.2.8.3
†† - P-value by Chi-square test, ** - P-value by Fisher's exact test
1) The percentage of subjects who showed complete remission up to 8 weeks and recurrence up to 24 weeks was presented.

- The time to recurrence from the complete remission up to 24 weeks

For the ITT analysis set, a recurrence-free survival rate was not decreased to less than 50% in both groups, which prevented estimation of the median time. The log-rank test to investigate whether there was a significant intergroup difference found that the recurrence-free survival rate of the test group was significantly higher than that of the control group at a 5% significance level (P-value=0.016).

For the PP analysis set, a recurrence-free survival rate was not decreased to less than 50% in both groups, which prevented estimation of the median time. The log-rank test found the recurrence-free survival rate of the test group was significantly higher than that of the control group at a 5% significance level (p-value=0.030). Source: Table

Table 4. The time to recurrence from the complete remission up to 24 weeks

	Test Group	Control Group	Total	P-value
ITT analysis set, n	67	69	136	
No. of subjects who showed complete remission until 8 weeks, n	53	53	106	
Time of subjects who showed recurrence after complete remission up to 24 weeks				
median time	-	-	-	0.016[1)]
95% CI	-	-	-	
PP analysis set, N	36	41	77	
No. of subjects who showed complete remission until 8 weeks, n	31	36	67	
Time of subjects who showed recurrence after complete remission up to 24 weeks				
median time	-	-	-	0.030 [1)]
95% CI	-	-	-	

Source: Appendix 13.2.6 and Appendix 13.2.8.3
1) P-value by Log-rank test

Safety Results:

In the study, the number of subjects who experienced adverse events during the study was 49 (73.13%) in the test group and 47 (68.12%) in the control group and there was no significant difference between 2 groups at a 5% significance level. The total number of adverse events was 127 in the test group and 133 in the control group. The number of subjects who experienced serious adverse events was 6 (9.00%) in the test group and 4 (6.00%) in the control group. The number of SAEs was 10 in the test group and 5 in the test group.

Table 5. Summary of adverse events reported during the study.

Adverse event	Test Group (n=67)	Control Group (n=69)	Total (n=136)
Number of subjects with adverse events (AEs), n(%)	49 (73.13)	47 (68.12)	96(70.59)
Number of AE	127	133	260
Serious adverse events (SAEs)			
Number of subjects with SAE, n(%)	6 (9.00)	4 (6.00)	10(7.35)
Number of SAE	10	5	15

Table continued on the next page

Table 5. continued

Assessment of AE cases			
Severity, n			
Mild	107	114	221
Moderate	18	17	35
Severe	2	2	4
Action taken with investigational drug, n			
No action	112	123	235
Dosage adjusted/temporarily interrupted	7	3	10
Permanently discontinued	8	7	15
Concomitant medication, n			
Yes	71	71	142
No	56	62	118
Relationship for investigational drug, n			
Definitely related	0	1	1
Probably related	8	12	20
Possibly related	35	24	59
Probably not related	64	65	129
Definitely not related	20	31	51
Outcome, n			
Recovered/resolved without sequelae	108	112	220
Recovered/resolved with sequelae	2	0	2
Not recovered/not resolved	8	14	22
Death	0	0	0
Unknown	9	7	16
Serious adverse event, n			
No	117	128	245
Yes	10	5	15
Hospitalization or prolonged hospitalization	10	5	15

Source: Appendix 13.2.7

The number of subjects with investigational drug-related adverse events was 26 (38.81%, 43 cases) in test group and 19 (27.54%, 37 cases) in control group. The most frequent drug-related adverse events were in the System Organ Class(SOC) 'Gastrointestinal disorders' in 14 subjects (20.9%, 18 cases) in test group and 8 subject (11.59%, 8 cases) in control group.

Table 6. Drug-related Treatment –emergent Adverse Events (MedDRA v15.0)

System Organ Class	Test Group (n=67)	Control Group (n=69)
Overall	26(38.81), 43	19(27.54), 37

Table continued on the next page

Table 6. continued

Cardiac disorders	1(1.49), 1	1(1.45), 1
Palpitations	1(1.49), 1	1(1.45), 1
Endocrine disorders	1(1.49), 1	1(1.45), 1
Cushingoid	1(1.49), 1	1(1.45), 1
Eye disorders	2(2.99), 2	0
Dry eye	1(1.49), 1	0
Visual impairment	1(1.49), 1	0
Gastrointestinal disorders	14(20.9), 18	8(11.59), 8
Abdominal pain	2(2.99), 2	0
Abdominal pain lower	1(1.49), 1	0
Abdominal pain upper	3(4.48), 3	0
Dental discomfort	0	1(1.45), 1
Diarrhoea	5(7.46), 6	0
Dyspepsia	2(2.99), 2	5(7.25), 5
Gastric ulcer	1(1.49), 1	0
Gastritis	0	1(1.45), 1
Gastrointestinal disorder	1(1.49), 1	0
Gastrointestinal pain	1(1.49), 1	1(1.45), 1
Vomiting	1(1.49), 1	0
General disorders and administration site conditions	4(5.97), 4	5(7.25), 6
Asthenia	1(1.49), 1	0
Face oedema	0	3(4.35), 3
Feeling cold	1(1.49), 1	0
Generalised oedema	2(2.99), 2	0
Oedema	0	1(1.45), 1
Oedema peripheral	0	2(2.9), 2
Infections and infestations	3(4.48), 3	4(5.8), 4
Bronchitis	0	1(1.45), 1
Folliculitis	0	1(1.45), 1
Herpes zoster	0	1(1.45), 1
Nasopharyngitis	1(1.49), 1	0
Pneumonia	1(1.49), 1	1(1.45), 1
Tuberculosis	1(1.49), 1	0
Investigations	0	1(1.45), 2
Alanine aminotransferase increased	0	1(1.45), 1
Aspartate aminotransferase increased	0	1(1.45), 1
Metabolism and nutrition disorders	2(2.99), 2	4(5.8), 4

Table continued on the next page

Table 6. continued

Diabetes mellitus	1(1.49), 1	1(1.45), 1
Hyperglycaemia	1(1.49), 1	3(4.35), 3
Musculoskeletal and connective tissue disorders	4(5.97), 5	5(7.25), 5
Arthralgia	2(2.99), 2	1(1.45), 1
Muscle spasms	2(2.99), 2	1(1.45), 1
Muscular weakness	0	1(1.45), 1
Myalgia	1(1.49), 1	2(2.9), 2
Nervous system disorders	2(2.99), 2	1(1.45), 1
Paraesthesia	1(1.49), 1	0
Tremor	1(1.49), 1	1(1.45), 1
Reproductive system and breast disorders	1(1.49), 1	0
Pruritus genital	1(1.49), 1	0
Skin and subcutaneous tissue disorders	3(4.48), 3	3(4.35), 4
Acne	0	1(1.45), 1
Alopecia	2(2.99), 2	1(1.45), 1
Hyperhidrosis	1(1.49), 1	0
Pruritus generalised	0	1(1.45), 1
Skin striae	0	1(1.45), 1
Vascular disorders	1(1.49), 1	1(1.45), 1
Flushing	1(1.49), 1	1(1.45), 1

Source: Appendix 13.2.7
Note) Number of subjects who experienced adverse events (%), number of cases

The number of subjects with investigational drug-related serious adverse events was 3 (4.48%, 3 cases) in test group and 1 subject (1.45%, 1 case) in control group. The most frequent drug-related SAEs were in the SOC Infections and Infestations in 2 subjects (2.99%, 2 cases) in test group and 1 subject (1.45%, 1 case) in control group.

Table7. Drug-related Serious Treatment-Emergent Adverse Events (MedDRA v15.0).

System Organ Class	Test Group (N=67)	Control Group (N=69)
Overall	3(4.48), 3	1(1.45), 1
Gastrointestinal disorders	1(1.49), 1	0
Gastrointestinal disorder	1(1.49), 1	0
Infections and infestations	2(2.99), 2	1(1.45), 1
Herpes zoster	0	1(1.45), 1
Pneumonia	1(1.49), 1	0
Tuberculosis	1(1.49), 1	0

Source: Appendix 13.2.7
Note) Number of subjects who experienced adverse events (%), number of case

The number of subjects with treatment-emergent adverse events other than serious adverse events was 47 (70.15%, 117 cases) in the test drug, and 46 (66.67%, 128 cases) in the control group. Threshold events with a frequency 5 percent or higher in a certain group which were treatment-emergent, were in the SOC Gastrointestinal Disorders, General Disorders and Administration Site Conditions, Infections and Infestations, Nervous System Disorders, and Respiratory, Thoracic and Mediastinal Disorders included 29 subjects (43.28%, 54 cases) in test group and 32 subjects (46.38%, 49 cases) in control group. Among them, the most frequent threshold events were in the SOC Gastrointestinal Disorders included 15 subjects (22.39%, 22 cases) in test group and 12 subjects (17.39%, 13 cases) in control group.

As for the actual measurements among laboratory test results, Hemoglobin, RBC, Hematocrit, Total cholesterol, Total Protein, Albumin, Total Bilirubin, AST (GOT), Serum Creatinine, LDL-cholesterol and Triglyceride was showed a statistically significant difference in change from baseline to Week 24 between the 2 treatment groups. There was no specific significant difference found in safety when comparing the test groups and control group.

CONCLUSIONS:

- The efficacy evaluation was conducted with the ITT set as the primary analysis group, and the PP set was secondarily analyzed. With both the IIT and PP analysis sets results considered, the primary efficacy evaluation has proved non-inferiority.
- As secondary efficacy evaluation, Period until the UPCR decreased to below 0.2 for the ITT and PP set was no significant difference in test and control groups. However, Percentage of subjects who showed recurrence after complete remission up to 24 weeks for the ITT and PP set in test group was lower than in the control group and a significant intergroup difference at a 5% significance level. Also The time to recurrence from the complete remission up to 24 weeks for the ITT and PP set was a significant intergroup difference, showing that the recurrence-free survival rate of the test group was significantly higher than that of the control group at a 5% significance level.
- There was no significant difference found in safety when comparing the groups with Tacrolimus combination with low-dose corticosteroid and with high-dose corticosteroid alone.
- An overall study conclusion on the efficacy and safety with low dose of steroid in combination with Tacrolimus is not inferior to high-dose corticosteroid alone for the treatment of MCNS and would be an effective treatment option.

Date of Report:

10 Mar 2018