

Appendix A: Extended Disability Status Scale (EDSS)

APPENDIX A

Kurtzke Expanded Disability Status Scale (EDSS)

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System (FS) score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS. Each step (e.g., 3.0 to 3.5) is still part of the DSS scale equivalent (i.e., 3). Progression from 3.0 to 3.5 should be equivalent to the DSS score of 3.

- 0 - Normal neurological exam (all grade 0 in FS).
- 1.0 - No disability, minimal signs in one FS (i.e., grade 1).
- 1.5 - No disability, minimal signs in more than one FS (more than on FS grade 1).
- 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1).
- 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.
- 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance: characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions): (usual FS equivalents are one grade

5 alone, others 0 or 1: or combinations of lesser grades usually exceeding specifications for step 4.0).

- 5.5 - Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities: (usual FS equivalents are one grade 5 alone, others 0 or 1: or combination of lesser grades usually exceeding those for step 4.0).
- 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting: (usual FS equivalents are combinations with more than two FS grade 3 +).
- 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting (usual FS equivalents are combinations with more than two FS grade 3 +).
- 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (usual FS equivalents are combinations with more than one FS grad 4 +; very rarely pyramidal grade 5 alone).
- 7.5 - Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair; (usual FS equivalents are combinations with more than one FS grade 4 +).
- 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions; generally has effective use of arms; (usual FS equivalents are combinations, generally grade 4 + in several systems).
- 8.5 - Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations generally 4 + in several systems).
- 9.0 - Helpless bed patient: can communicate and eat; (usual FS equivalents are combinations, mostly grade 4 +).
- 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, almost all grade 4 +).
- 10.0 - Death due to MS.

Appendix B: Ambulation Index (AI)

APPENDIX B

Ambulation Index (AI)

- 0 = Asymptomatic; fully active.
- 1 = Walks normally but reports fatigue which interferes with athletic or other demanding activities.
- 2 = Abnormal gait or episodic imbalance; gait disorder is noticeable to family and friends. Able to walk 8 meters in 10 seconds or less.
- 3 = Walks independently; able to walk 8 meters in 20 seconds or less.
- 4 = Requires unilateral support (cane, single crutch) to walk; walks 8 meters in 20 seconds or less.
- 5 = Requires bilateral support (canes, crutches, walker) and walks 8 meters in 20 seconds or less; or, requires unilateral support but walks 8 meters in greater than 20 seconds.
- 6 = Requires bilateral support and walks 8 meters in greater than 20 seconds. May use wheelchair on occasion.
- 7 = Walking limited to several steps with bilateral support; unable to walk 8 meters. May use wheelchair for most activities.
- 8 = Restricted to wheelchair; able to transfer independently.
- 9 = Restricted to wheelchair; unable to transfer independently.

Appendix C: Standard Neurological Status (SNS)

APPENDIX C

Standardized Neurologic Status (SNS)

		Total Score	
I. Definite Supraspinal Signs			
<input type="checkbox"/>	Vision (right) (quantitative)	0 = ≥ 1.0 1 = ≤ 0.9 2 = ≤ 0.7	
<input type="checkbox"/>	Vision (left) (quantitative)	3 = < 0.5 4 = ≤ 0.3 5 = ≤ 0.1	
<input type="checkbox"/>	Ocular motor nerve palsy/Gaze palsy	0 = absent 1 = in 1 line of vision 2 = in > 1 line of vision	
<input type="checkbox"/>	Spontaneous nystagmus	0 = absent 1 = present	
<input type="checkbox"/>	Gaze evoked nystagmus	0 = absent 1 = present	
<input type="checkbox"/>	Dissociated nystagmus/INOP	0 = absent 1 = present	
<input type="checkbox"/>	Speech impairment (bulbar/cerebellar)	0 = absent 1 = mild 2 = speech only intelligible with great effort	
<input type="checkbox"/>	Swallowing	0 = not impaired 2 = slightly impaired 4 = frequent deglutition disturbances/coughing	
<input type="checkbox"/>	Breathing	0 = not impaired 6 = impaired	
<input type="checkbox"/>	Intention tremor/nonparetic dysmetria	0 = absent 1 = mild (motor response not impaired) 2 = moderate (motor response noticeably impaired) 3 = severe (e.g., hands can no longer be used)	
<input type="checkbox"/>	Truncal ataxia	0 = absent 2 = mild 4 = moderate (unaided sitting with arms stretched out just barely possible) 8 = severe (unaided sitting no longer possible)	
<input type="checkbox"/>	Ataxic gait	0 = absent 8 = present	
<input type="checkbox"/>	Affect	0 = not impaired 1 = impaired	
<input type="checkbox"/>	Drive/motivation	0 = not impaired 1 = slightly impaired 3 = severely impaired	
<input type="checkbox"/>	Psycho-motor slowing		
II. Paresis			
<input type="checkbox"/>	Right arm/hand	5 = no muscle activity 4 = visible muscle contraction without movement	
<input type="checkbox"/>	Left arm/hand	3 = locomotive effect seen when at rest 2 = motion possible against no resistance 1 = motion possible against moderate resistance 0 = normal muscle strength	
<input type="checkbox"/>	Right leg/foot		
<input type="checkbox"/>	Left leg/foot		
III. Spasticity			
<input type="checkbox"/>	Right arm	0 = absent 1 = increase in tone may be overcome in rapid continuous movement 2 = spasticity may be overcome only very slowly and with great effort	
<input type="checkbox"/>	Left arm		
<input type="checkbox"/>	Right leg		
<input type="checkbox"/>	Left leg		
IV. Sensation			
<input type="checkbox"/>	Abdomen	<u>Sense of touch:</u> 0 = not impaired 1 = impaired	
<input type="checkbox"/>	Right arm/hand		
<input type="checkbox"/>	Left arm/hand		
<input type="checkbox"/>	Right leg/foot		
<input type="checkbox"/>	Left leg/foot		
<input type="checkbox"/>	Right malleolus ext.	<u>Sensitivity to vibrations:</u> 0 = > 6/8 1 = $\leq 6/8$ 2 = $\leq 3/8$	
<input type="checkbox"/>	Left malleolus ext.		
V. Urinary Bladder Impairment			
<input type="checkbox"/>	Urgency	0 = absent 1 = present	
<input type="checkbox"/>	Urinary incontinence	0 = absent 1 = rarely 3 = about weekly 4 = severe (diapers or urinal required)	
<input type="checkbox"/>	Overflow incontinence (Ischuria paradoxa)	0 = absent 1 = present	
<input type="checkbox"/>	Indwelling catheter/suprapubic drain	0 = absent 1 = present	
<input type="checkbox"/>	Residual urine	0 = ≤ 50 ml 1 = < 100 ml 2 = ≥ 100 ml x = not done	

**Appendix D: Summary of Preclinical Studies in Experimental Allergic
Encephalomyelitis (EAE)**

APPENDIX D

Summary of Preclinical Studies in Experimental Allergic Encephalomyelitis (EAE)

Mitoxantrone has been shown to be effective in a variety of EAE models. Major findings from the studies of mitoxantrone in EAE are summarized in the table that follows.

Results obtained using active models of EAE are categorized as prophylactic effects (mitoxantrone treatment beginning at the time of immunization), effector-level inhibition (treatment beginning after effector cells are primed but before disease onset is evident), or therapeutic protection (treatment beginning after disease has been clearly established).

Summary of EAE Study Results

Study	Type of EAE model	Mitoxantrone treatment regimen	Results
<i>Therapeutic Protection in Active EAE Models</i>			
Levine, 1985	Relapsing disease Lewis rats	1 mg/kg IP or SC (leg) Single dose Day 14	All 6 control rats relapsed. Mitox prevented relapse in 12 of 14 rats.
Watson, 1991	Relapsing disease Biozzi AB/H mice	2.5 mg/kg IP, twice weekly Days 27-40	Mitox prevented relapse in 12/13 mice (p < 0.002).
<i>Effector-Level Inhibition in Active EAE Models</i>			
Ridge, 1985	Acute disease Lewis rats	0.25 – 0.5 mg/kg/day IP Days 7-16 Compared to 1.25 – 5.0 mg/kg CP	Mitox at 0.25 – 0.5 mg/kg suppressed clinical and histological lesions (p < 0.05).
Watson, 1991	Acute disease Biozzi AB/H mice	1 – 2.5 mg/kg/day IP Days 12-19	Mitox at 2.5 mg/kg prevented development of acute disease.
Baker, 1992	Acute disease Biozzi AB/H mice	0.5 – 5.0 mg/kg IP Single dose Day 9	A single dose of 5 mg/kg Mitox completely inhibited the development of EAE.
<i>Prophylactic Effects in Active EAE Models</i>			
Ridge, 1985	Acute disease Lewis rats	0.125 – 0.5 mg/kg/day IP for 16 days starting on Day 0. Compared to 1.25 – 5.0 mg/kg	Mitox at 0.25 – 0.5 mg/kg suppressed clinical and histological lesions (p < 0.05).
Lublin, 1987	Acute disease (SJL/J x BALB/c) F1 mice	0.25 or 0.5 mg/kg/day IP 10 days starting on Day 0	Mitox prevented the development of EAE.
Lublin, 1987	Delayed onset disease SJL/J mice	0.05 mg/kg IP 3x/week for 12 weeks.	Mitox significantly delayed the onset of disease.
Mustafa, 1993	Acute disease Lewis rats	0.5 mg/kg IP, alternate days (Days 0-15). Compared to CsA at 3.0 or 20 mg/kg, alternate days (Days 0-22)	Mitox completely protected rats from EAE.
<i>Treatment of Passive EAE</i>			
Ridge, 1985	Lewis rats immunized with sensitized, syngeneic immune cells	<ul style="list-style-type: none"> • Donors: 0.5 mg/kg/day x 14 days • Cells in vitro: 0.01-0.001 mg/mL • Recipient pretreatment: 0.5 mg/kg/day IP x 5 days 	Mitox prevented the development of passive EAE in all three experimental designs.

Mitox = mitoxantrone; CP = cyclophosphamide; CsA = cyclosporine A.

References for EAE Study

Baker D, O'Neill JK, Davison AN, et al. Control of immune-mediated disease of the central nervous system requires the use of a neuroactive agent: elucidation by the action of mitoxantrone. *Clin Exp Immunol* 1992;90:124-128.

Levine S, Saltzman A. Regional suppression, therapy after onset and prevention of relapses in experimental allergic encephalomyelitis by mitoxantrone. *J Neuroimmunol* 1985;13:175-181.

Lublin FD, Lavassa M, Viti C, et al. Suppression of acute and relapsing experimental allergic encephalomyelitis with mitoxantrone. *Clin Immunol and Immunopathol* 1987;45:122-128.

Mustafa MD, Diener P, Sun JB, et al. Immunopharmacologic modulation of experimental allergic encephalomyelitis: low-dose cyclosporin-A treatment causes disease relapse and increased systemic T and B cell-mediated myelin-directed autoimmunity. *Scand J Immunol* 1993;38:499-507.

Ridge SC, Sloboda AE, McReynolds RA, et al. Suppression of experimental allergic encephalomyelitis by mitoxantrone. *Clin Immunol Immunopathol* 1985;35:35-42.

Watson CM, Davison AN, Baker D, et al. Suppression of demyelination by mitoxantrone. *Int J Immunopharmacol* 1991;13:923-930.

**Appendix E: Statistical Methodology for the Primary Efficacy Analysis
in Study 901**

APPENDIX E

Statistical Methodology for the Primary Efficacy Analysis in Study 901

Three methodological approaches can be used for clinical studies with multiple primary endpoints to produce a statistical analysis that protects the experiment-wise error rate:

1. Combine the attributes of all primary endpoints into a single composite endpoint and perform an analysis of this composite endpoint using the predefined alpha level.
2. Adjust the alpha level, usually by a Bonferroni adjustment, and perform separate analyses of each primary endpoint using the adjusted alpha level.
3. Perform a multivariate analysis using the predefined alpha level.

For Study 901, there was no generally acceptable composite score that could be adopted. Further, a Bonferroni adjustment was impractical due to the large number of endpoints. With the approval of the German regulatory agency BfArM, a nonparametric multivariate statistical analysis was specified in the protocol to establish primary efficacy results. This statistical methodology, described below, has been published in preeminent American statistical journals, and shown to be statistically valid. Validated, commercially available software (SmarTest 1995) has been developed to perform this analysis. The FDA has been provided with a copy of this software, along with documentation and validation information, for review.

The five primary efficacy variables for Study 901 were:

- Change in EDSS at 24 months relative to baseline value.
- Change in AI at 24 months relative to baseline value.
- Number of relapses requiring corticosteroid treatment.
- Time to the first relapse requiring corticosteroid treatment.

- Change in SNS score at 24 months relative to baseline value.

These efficacy variables were tested in one combined hypothesis of stochastic ordered alternatives by the generalized Wilcoxon-Mann-Whitney (Wei-Lachin) procedure (Lachin 1992, Wei 1984). The test was to be conducted for a one-sided hypothesis with $\alpha = 0.05$ for the difference between the mitoxantrone 12 mg/m² treatment group and placebo group. This is a nonparametric global test, hypothesizing that the differences between groups are all in the same direction; i.e., one group is superior in at least one of the variables.

The hypotheses stated in this test are:

$$H_0 : \Theta_k = 0 \quad \text{for all } k=1,2,3,4,5 \quad (\text{variables tested})$$

$$H_1 : \Theta_k \geq 0 \quad \text{for all } k=1,2,3,4,5 \quad \text{with } \Theta_k > 0 \text{ for at least one } k.$$

The Θ_k are the estimators of the difference between the two samples, the Mann-Whitney differences. A Mann-Whitney difference is defined as the difference between (1) the probability that a member of sample 1 has a larger value for the variable of interest than a member of sample 2 and (2) the probability that a member of sample 2 has a larger value for the variable of interest than a member of sample 1.

The Mann-Whitney difference is also a valid estimator for variables with missing values or censored observations such as the variable “time to first relapse requiring treatment.”

The test statistic Z derived from the Wei-Lachin procedure has an asymptotic normal distribution and is defined as:

$$Z = (J' \Theta) / [J' \Sigma J]^{1/2}$$

with Σ being the covariance-matrix of Θ and $J'=(1,\dots,1)$, a vector of weights one.

This test statistic is the nonparametric equivalent to Hotelling’s one-sided parametric T² test. If the test resulted in a significant p-value, all five single criteria were to be tested

univariately with $\alpha = 0.05$ in sequence according to the principle of a priori ordered hypotheses (Maurer 1995). The sequence of testing was revised by Amendment 3 to be EDSS, AI, number of relapses requiring corticosteroid treatment, time to the first relapse requiring such treatment, and SNS. In this document, results of two-sided tests are reported with $\alpha = 0.05$.

References

Lachin JM. Some large-sample distribution-free estimators and tests for multivariate partially incomplete data from two populations. *Stat Med* 1992; 11:1151-70.

Maurer W, Hothorn LA, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: A-priori ordered hypothesis. In: *Biometrie in der chemisch-pharmazeutischen industrie 6: Testing principles in clinical and preclinical trials* (Vollmar J, ed.). Gustav Fischer Verlag, Stuttgart 1995:3-18.

SmarTest Handbook Version 1.2, idv – Datenanalyse und Versuchspannung, Gauting – Germany, 1995.

Wei LJ, Lachin JM. Two-sample asymptotically distribution-free tests for incomplete multivariate observations. *J Am Stat Assoc* 1984; 79(387):653-61.

Appendix F: Summary of Sensitivity Analyses Conducted in Study 901

APPENDIX F

Summary of Sensitivity Analyses Conducted in Study 901

Post-hoc sensitivity analyses were performed on various patient subgroups. This summary provides data from the mitoxantrone 12 mg/m² and placebo groups only and is limited to the analysis of the primary efficacy variables. These analyses were consistent with the efficacy results seen in the population as a whole and confirmed the superiority of mitoxantrone compared to placebo.

Gender Effect

Analysis of Gender Effect

Endpoint	Female		Male	
	Placebo N = 31	Mitox 12 mg/m ² N = 28	Placebo N = 33	Mitox 12 mg/m ² N = 32
EDSS change (mean, M24 minus baseline)*	0.08	-0.46	0.36	0.16
AI change (mean, M24 minus baseline)*	0.61	0	0.91	0.56
SNS change (mean, M24 minus baseline)*	1.29	-2.50	0.27	0.19
No. treated relapses (total, adjusted for early withdrawals)	43.59	6.28	33.18	17.80
Time to 1 st relapse requiring treatment (median months)	11.10	NR	NR	NR

Mitox = mitoxantrone; NR = median not reached within 24 months.

* Negative values indicate improvement for this scale, higher positive values indicate worsening.

Age Effect

Patients were evaluated based on a age cutoff of 40, median age for this study population.

Analysis of Age Effect

Endpoint	< 40 Years		≥ 40 Years	
	Placebo N = 32	Mitox 12 mg/m ² N = 31	Placebo N = 32	Mitox 12 mg/m ² N = 29
EDSS change (mean, M24 minus baseline)*	-0.03	-0.37	0.48	0.12
AI change (mean, M24 minus baseline)*	0.72	0.06	0.81	0.55
SNS change (mean, M24 minus baseline)*	-0.13	-1.58	1.66	-0.52
No. treated relapses (total, adjusted for early withdrawals)	38.74	14.08	38.03	10.00
Time to 1 st relapse requiring treatment (median months)	15.01	NR	14.19	NR

Mitox = mitoxantrone; NR = median not reached within 24 months.

* Negative values indicate improvement for this scale, higher positive values indicate worsening.

Type of MS

Patients were evaluated based on the type of MS as defined in the protocol.

Analysis Based on Type of MS

Endpoint	Remitting Progressive		Secondary Progressive	
	Placebo N = 10	Mitox 12 mg/m ² N = 17	Placebo N = 23	Mitox 12 mg/m ² N = 15
EDSS change (mean, M24 minus baseline)*	0.09	-0.30	0.34	0.02
AI change (mean, M24 minus baseline)*	0.41	0.14	1.06	0.44
SNS change (mean, M24 minus baseline)*	-0.31	-2.46	1.66	0.16
No. treated relapses (total, adjusted for early withdrawals)	45.61	8.61	31.17	15.47
Time to 1 st relapse requiring treatment (median months)	11.10	NR	21.95	NR

Mitox = mitoxantrone; NR = median not reached within 24 months.

* Negative values indicate improvement for this scale, higher positive values indicate worsening.

Relapse 1 Year Prior to Study

Patients were evaluated based on whether they had a history of relapse(s) in the year preceding enrollment or not.

Relapse 1 Year Prior to Study

Endpoint	Yes		No	
	Placebo N = 22	Mitox 12 mg/m ² N = 25	Placebo N = 11	Mitox 12 mg/m ² N = 7
EDSS change (mean, M24 minus baseline)*	0.05	-0.22	0.67	0.13
AI change (mean, M24 minus baseline)*	0.61	0.20	1.17	0.60
SNS change (mean, M24 minus baseline)*	-0.74	-1.78	4.61	2.33
No. treated relapses (total, adjusted for early withdrawals)	58.81	20.34	17.96	8.78
Time to 1 st relapse requiring treatment (median months)	13.83	25.30	15.38	NR

Mitox = mitoxantrone; NR = median not reached within 24 months.

* Negative values indicate improvement for this scale, higher positive values indicate worsening.

Study Completers

Patients were evaluated based on whether they completed all eight course of study drug (completers) or not (i.e., intent-to-treat group)

Study Completers

Endpoint	Completers		Intent to Treat	
	Placebo N = 23	Mitox 12 mg/m ² N = 24	Placebo N = 33	Mitox 12 mg/m ² N = 32
EDSS change (mean, M24 minus baseline)*	0.14	-0.25	0.23	-0.13
AI change (mean, M24 minus baseline)*	0.66	0.25	0.77	0.30
SNS change (mean, M24 minus baseline)*	0.60	-0.88	0.77	-1.07
No. treated relapses (total, adjusted for early withdrawals)	46.33	13.23	76.77	24.08
Time to 1 st relapse requiring treatment (median months)	16.20	25.30	14.2	NR

Mitox = mitoxantrone; NR = median not reached within 24 months.

* Negative values indicate improvement for this scale, higher positive values indicate worsening.

APPENDIX G

Published Papers

This appendix contains reprints of the following papers:

Bastianello S, Pozzilli C, D'Andrea F, et al. A controlled trial of mitoxantrone in multiple sclerosis: Serial MRI evaluation at one year. *Can J Neurol Sci* 1994; 21:266-70.

De Castro S, Cartoni D, Millefiorini E, et al. Noninvasive assessment of mitoxantrone cardiotoxicity in relapsing remitting multiple sclerosis. *J Clin Pharmacol* 1995; 35:627-32.

Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: A randomized multicentre study of active disease using MRI and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997;62:112-8.

Hartung H-P, Gonsette R, MIMS Study Group. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, randomized, observer-blind phase III trial: clinical results and three-year follow-up. *Neurology* 1999a;52(Suppl 2):A290. (Abstract S45.005).

Hartung H-P, Gonsette R, MIMS Study Group. Mitoxantrone in progressive multiple sclerosis (MS): Clinical results and three-year follow-up of the MIMS trial. *Mult Scler* 1999;5(Suppl 1):S15. (Abstract 56).

Hartung H, Gonsette R, MIMS Study Group. Mitoxantrone in progressive multiple sclerosis (MS): A placebo-controlled, randomized, observer-blind European phase III multicenter study -- Clinical results. *Mult Scler* 1998;4:98. (Abstract 207).

Krapf H, Morrissey SP, Zenker O, et al. Mitoxantrone in progressive multiple sclerosis (MS): A placebo-controlled, randomized, observer-blind European phase III multicenter study -- MRI results. *Mult Scler* 1998;4:380. (Abstract P3024).

Millefiorini E, Gasperini C, Pozzilli C, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997;244:153-9.

Appendix G: Published Papers

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