Results from a Pivotal Phase 3, DB, R, Placebo-controlled, Multicenter Trial of SP-102, a Novel Dexamethasone Injectable Formulation, for the Treatment of Patients with Lumbosacral Radiculopathy (Sciatica)

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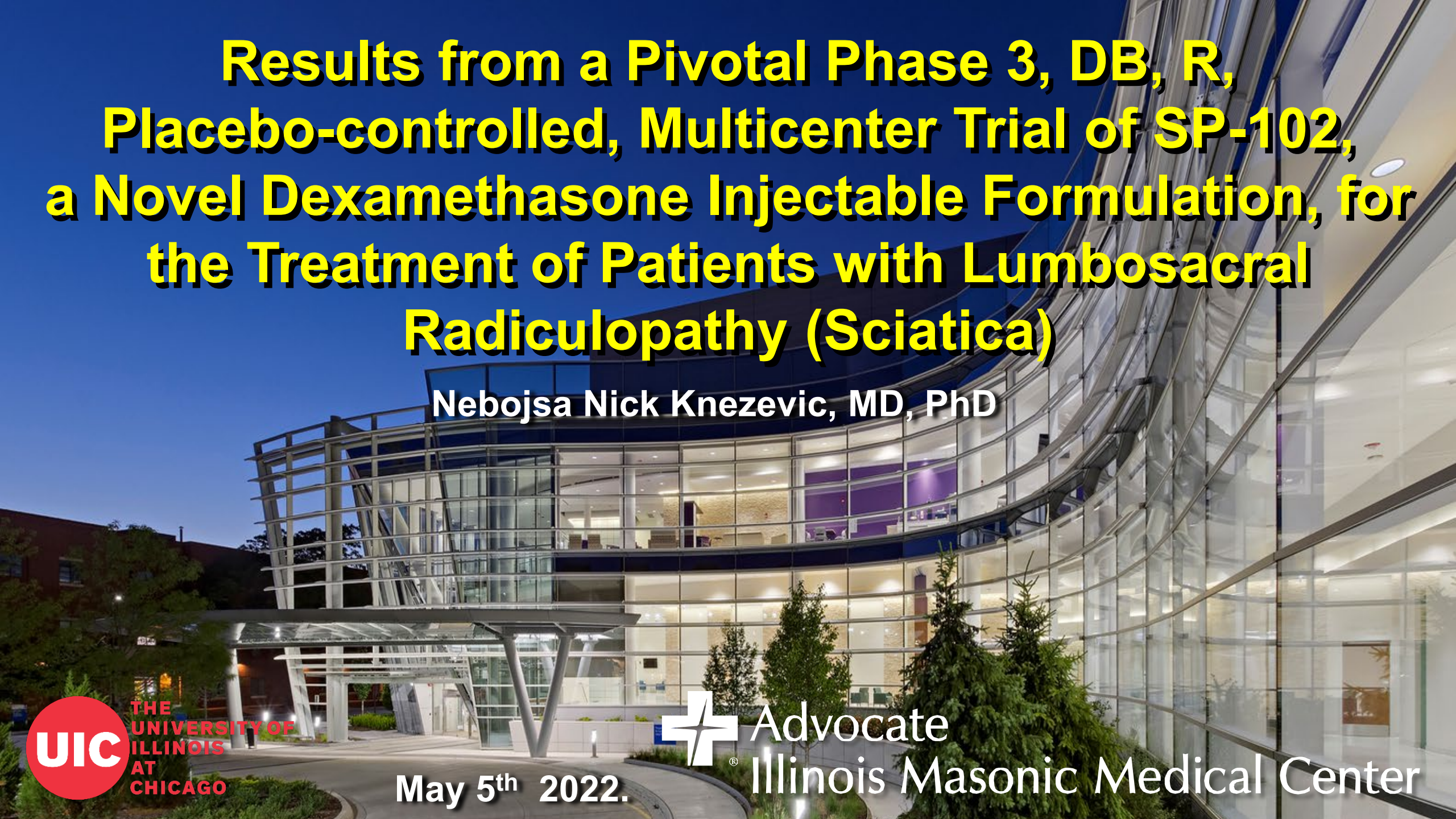

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Disclaimer

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Summary of Select Systematic Reviews and Meta-analyses

Type	Publication	Intervention	Outcomes		
			Improvement in Pain	Improvement in Function	Surgery Avoidance
RCT	Carette 1997	ESI vs Placebo	🟡	🔴	🔴
Meta-analysis	Chou 2015	ESI	🟡	🟡	🟡
Meta-analysis	Bhatia 2016	ESI +/- Local Anesthetic	🟡	🔴	🔴
Systematic Review	Kaye 2015	ESI +/- Local Anesthetic	🟢	🟢	🟢
Systematic Review	Manchikanti 2016	ESI +/- Local Anesthetic	🟢	🟢	
Systematic Review	Oliviera 2020	ESI +/- Local Anesthetic	🟡	🟡	
Systematic Review	Smith 2020	ESI +/- Local Anesthetic	🟢		

🟢 Clinically significant improvement

🟡 Short-term improvement only and/or not clinically meaningful

🔴 No improvement

References

Carette S, et al. NEJM 1997;336:1634-40

Bhatia A, et al. Anesth Analg 2016;122:857-70

Smith CC, et al. Pain Medicine 2020;21(3):472-487

Oliveira CB, et al. Cochrane Database of Systematic Reviews 202 Apr 9; 4(4)

Manchikanti L, et al. Pain Physician 2016;19:E365-E410

Kaye A, et al. Pain Physician 2015;18:E939-1004

Chou R, et al. Annals of Internal Medicine 2015;163(5):373-81

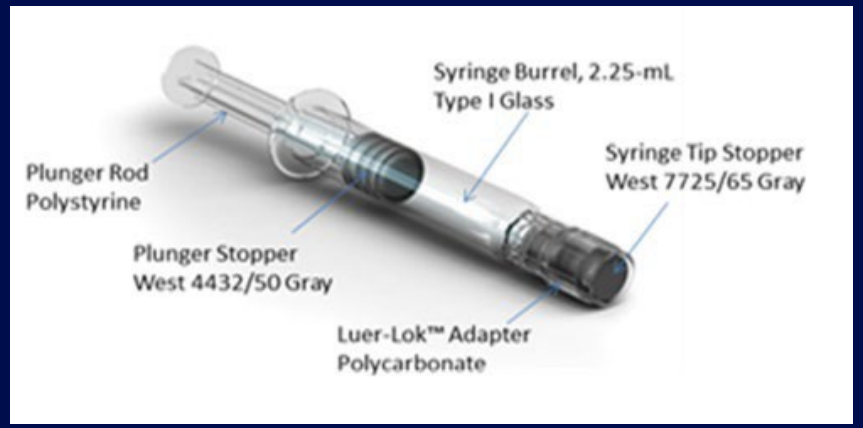
History of Serious Spinal Adverse Events (SSAEs) with Current ESIs

1997-2014	90 serious (including fatal) neurological events following ESIs reported to FAERS[1]
2014	FDA required warning for all injectable corticosteroid product labels[2]
2015	FDA convened panel of experts (Multidisciplinary Working Group –MWG) for Safe Use Initiative (SUI) to review existing evidence regarding neurological complications and publish recommendations to prevent neurological complications after ESIs[3]

1. Racoosin JA, Seymour SM, Cascio L, et al. Serious neurologic events after epidural glucocorticoid injection—The FDA's Risk Assessment. *N Engl J Med*. 2015;373:2299–2301
2. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-label-changes-warn-rare-serious-neurologic-problems-after#:~:text=%5B04%2D23%2D2014%5D,stroke%2C%20paralysis%2C%20and%20death.
3. Rathmell JP, et al. Safeguards to prevent neurologic complications after epidural steroid injections. Anesthesiology 2015; 122(5): 974-84

SP-102 – Product Characteristics

- Potent non-particulate steroid (injectable dexamethasone sodium phosphate viscous gel)
- Pre-filled syringe for epidural use
- Gel formulation for extended local release and substantial magnitude of pain relief
- Well-tolerated, Key viscous excipient, long history of use including safety
- Fast acting onset of effect with less spread and safer repeat injections
- No preservatives, no surfactants, no particulates. Non-opioid and non-addictive
- Projected 24-month shelf life



C.L.E.A.R. (Corticosteroid Lumbar Epidural Analgesia for Radiculopathy) Trial Objectives

Primary Objective:

- Evaluate the analgesic effect on average daily leg pain (as measured by the NRPS in the affected leg) following a single TF injection of SP-102 compared to an i.m. injection of placebo over 4 weeks.

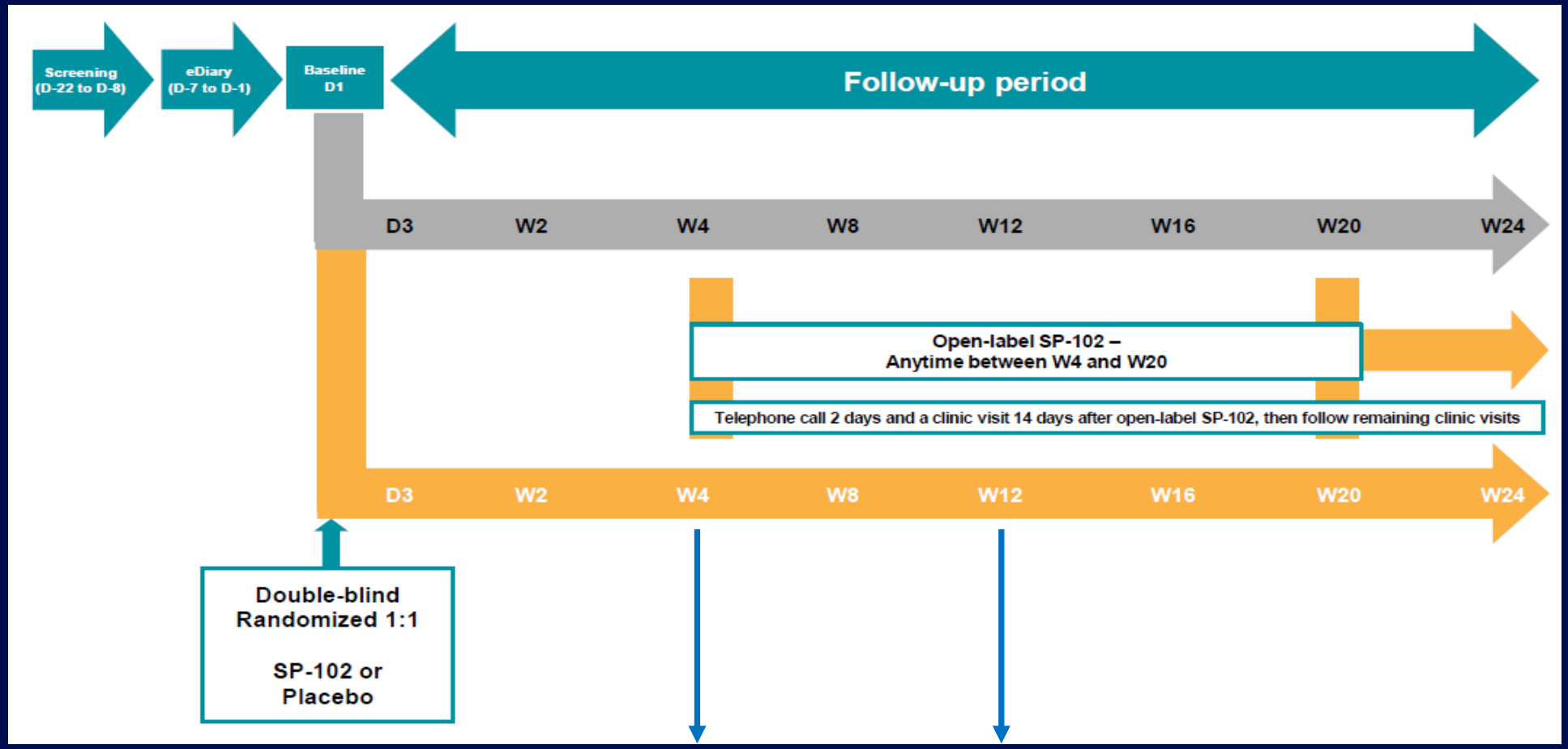
Secondary Objectives:

- Evaluate the degree of disability over time as measured by the ODI
- Characterize the change of the subject's radiculopathy symptoms and overall condition using PainDETECT, BPI-SF, CGIC, and PGIC
- Evaluate the safety of single and repeat SP-102 TF injections

C.L.E.A.R. Trial Design

Inclusion

- ✓ Radicular leg pain episode (4-9 NPRS) **6 weeks-9 months**
- ✓ MRI confirmed within 9 months
- ✓ No prior ESI
- ✓ No opioids or NSAIDs
- ✓ Stable, >4 avg NPRS pain in 21d screening



Primary Endpoint
Change in mean leg pain (NPRS) over first 4 weeks

Secondaries (W2, W4, W8, W12) Leg pain (NPRS, avg & worst pain), disability (ODI), time to repeat injection

Subject Disposition

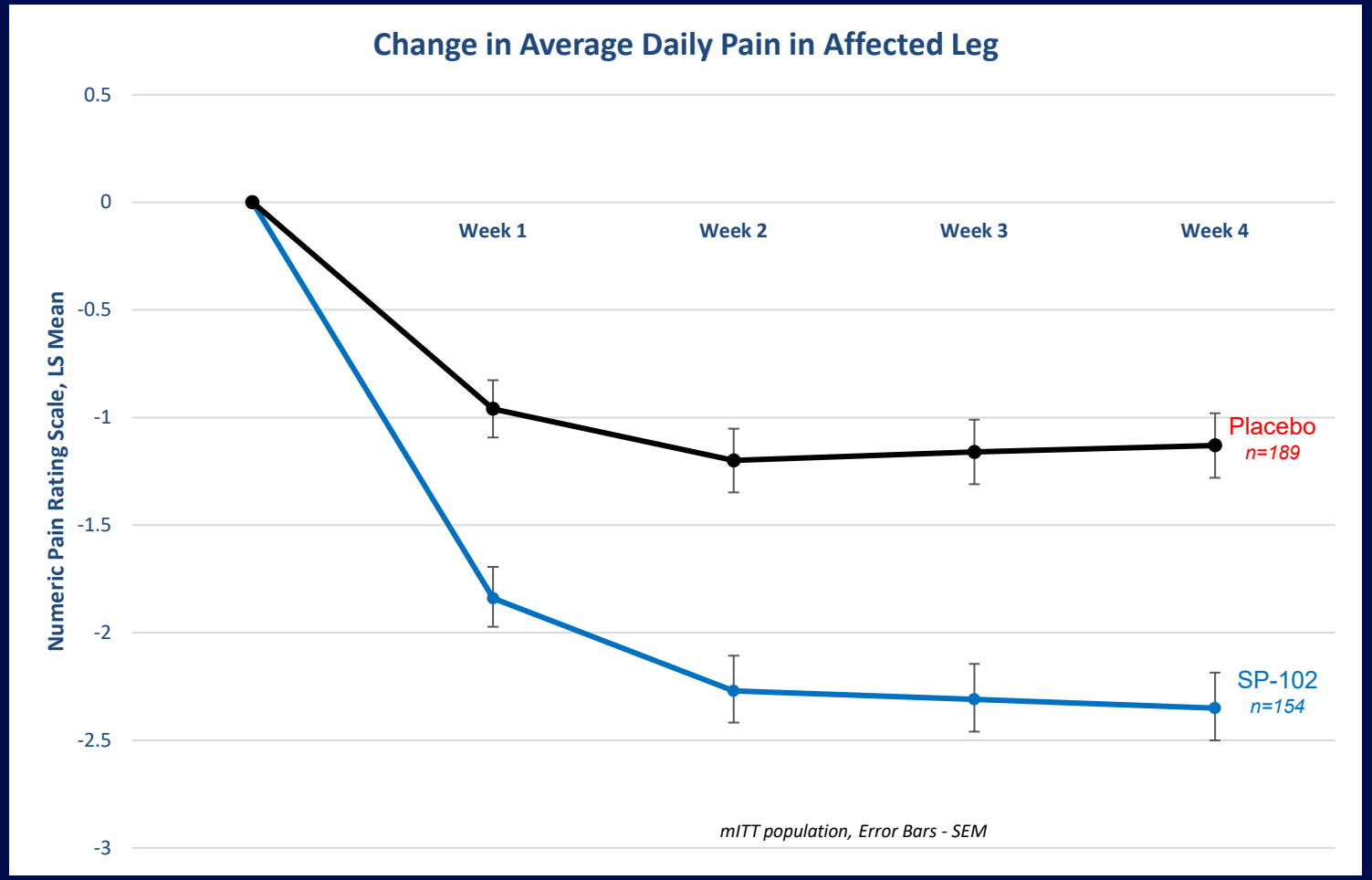
	SP-102	Placebo	Overall
Screened			2048
Screen failures[1]			1647 (80.4%)
Randomized (Safety Analysis Population)	**202**	**199**	**401**
Week 4 completers	193 (95.5%)	192 (96.5%)	385 (96.0%)
Early Terms by Week 4	5 (2.5%)	4 (2.0%)	9 (2.2%)
IP injection administered in correct anatomical location (mITT)	**154 (76.2%)**	**189 (94.9%)**	**343 (85.5%)**
Per Protocol Population	153 (75.7%)	187 (94.0%)	340 (84.8%)
Week 12 completers			355 (88.5%)
Week 24 completers			340 (84.8%)

[1]Screen failures mostly due to not meeting randomization criteria (93.6%)

Demographics

	SP-102 (n=202)	Placebo (n=199)	Overall (n=401)
Mean age at Screening (SD)	51.2 (9.83)	51.7 (10.36)	51.4 (10.09)
Sex			
Female	116 (57.4%)	122 (61.3%)	238 (59.4%)
Male	86 (42.6%)	77 (38.7%)	163 (40.6%)
Race			
White	160 (79.2%)	162 (81.4%)	322 (80.3%)
Black or African American	37 (18.3%)	33 (16.6%)	70 (17.5%)
Asian	4 (2.0%)	3 (1.5%)	7 (1.7%)
Mean Weight, kg (SD)	86.33 (17.81)	85.51 (16.67)	85.92 (17.24)
Mean BMI, kg/m^2 (SD)	29.90 (5.30)	29.79 (5.03)	29.85 (5.16)
Mean Height, cm (SD)	169.76 (10.55)	169.32 (9.88)	169.54 (10.21)

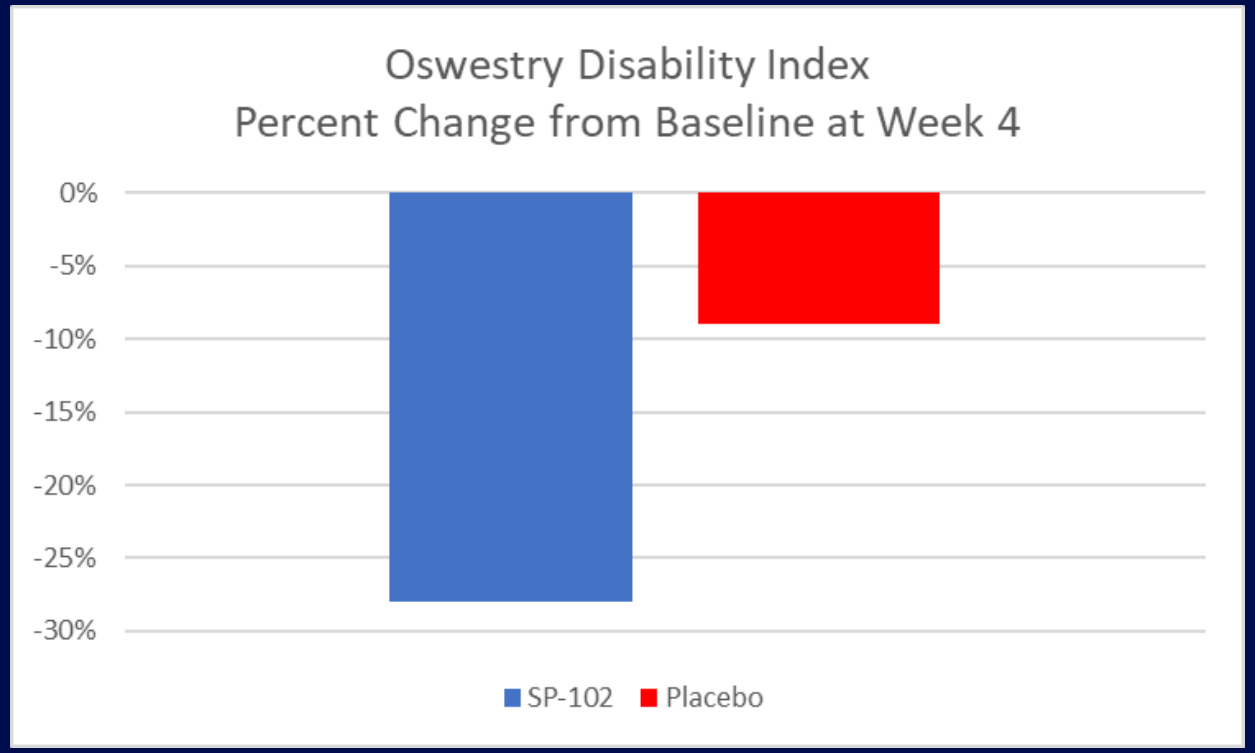
C.L.E.A.R. Trial – Primary Endpoint



Comparison: SP-102 vs. Placebo	
Over 4 Weeks, LS Mean (SE)	-1.08 (0.17)
95% CI	-1.42, -0.75
p-value	<0.001***

The analysis used a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM) with fixed effects for treatment (SP-102 or placebo), week, site, Pain Catastrophizing Scale group (<30 or ≥30), baseline averaged daily leg pain score, and treatment-by-week interaction.

Key Secondary Endpoint - ODI



ODI (mITT)	SP-102 N= 154	Placebo N=189
Baseline, Mean (SD)	38.95 (12.721)	39.92 (13.002)
Week 4, Mean (SD)	28.36 (15.633)	34.57 (16.687)

Comparison	
LS Mean (SE)	-6.28 (1.494)
95% CI	-9.22, -3.34
p-value	<0.001***

ANCOVA model with change from baseline in ODI score at Week 4 as the response variable and treatment (SP-102 or placebo), site, and Pain Catastrophizing Scale group (<30 or ≥30) as fixed effects, and baseline ODI as covariate. Table 14.2.2.1.1.

Global Impression of Change

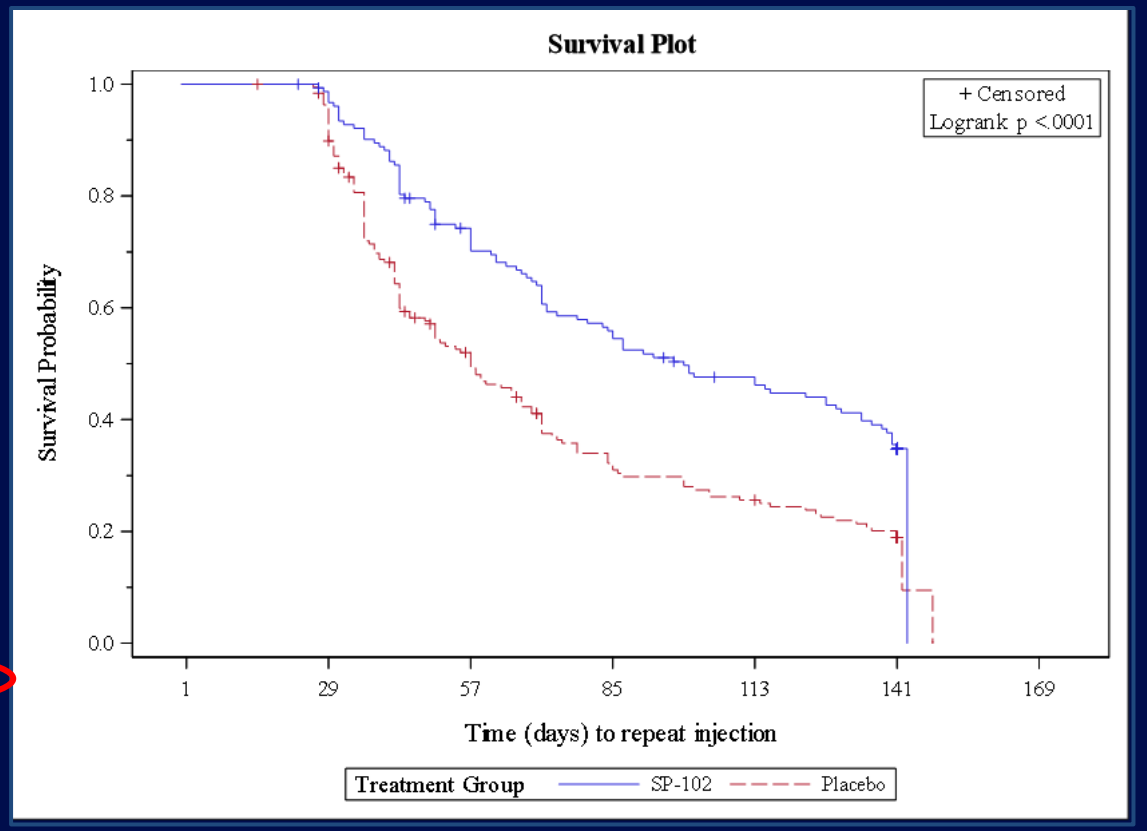
at Week 4 (mITT)	SP-102 N= 154	Placebo N=189
Patient Global Impression of Change, Number of Responders	68 (**44.2%**)	34 (**18.0%**)
Chi-Square: p-value **<0.001*** **		
Logistic Regression: Odds Ratio (95% CI) - 3.81 (2.32, 6.27) p-value <0.001***		
Clinical Global Impression of Change, Number of Responders	72 (**46.8%**)	34 (**18.0%**)
Chi-Square: p-value **<0.001*** **		
Logistic Regression: Odds Ratio (95% CI) - 4.24 (2.58, 6.98) p-value <0.001***		

Logistic regression models with treatment (SP-102 or placebo), site, and Pain Catastrophizing Scale group (<30 or ≥30) as factors were used to compare the treatment groups at each week.

A responder is a subject with a response of 1: very much improved or 2: much improved, and a non-responder if the response is all other responses (recorded as 3, 4, 5, 6, or 7) in the scale. Subjects who did not complete the measure at the timepoint of interest were considered non-responders. Table 14.2.3.1, 14.2.14.1

Time (days) to Repeat Injection of SP-102

	SP-102 N= 154	Placebo N=189
Number of subjects with repeat injection of SP-102	97 (**63.0%**)	146 (**77.2%**)
Number of censored subjects	57 (37.0%)	43 (22.8%)
Time (days) to Repeat Injection		
25th quantile (95% CI)	50 (43, 62)	36 (34, 39)
50th quantile (95% CI)	**99 (78, 129)**	**57 (49, 67)**
75th quantile (95% CI)	143 (NE, NE)	116 (85, 148)



Comparison to Placebo
Hazard Ratio (95% CI) 0.56 (0.43, 0.73)
p-value <0.001***
Chi-Square p-value 0.004**

Censored subjects: 1. subjects who do not receive a repeat injection of SP-102 and 2. subjects who discontinued the study prior to Week 20 without receiving a repeat injection. Survival Probability used Kaplan-Meier estimation. NE = Not Estimable.

A Cox proportional hazards model was utilized to test the treatment difference in time to repeat injection while adjusting for site and Pain Catastrophizing Scale (<30 or ≥30).

Tables 14.2.4.1, 14.2.4.1.1, 14.2.5.1

Mean Daily NPRS, Pain DETECT, and BPI-SF

Change from Baseline to 4 weeks	LS Mean (SE)	95% CI	p-value
Worst Pain in Affected Leg[1]	-1.23 (0.210)	-1.65, -0.82	<0.001***
Current Pain in Affected Leg[1]	-1.3 (0.25)	-1.8, -0.8	<0.001***
Average Pain in Lower Back[1]	-1.0 (0.24)	-1.4, -0.5	<0.001***
PainDETECT[2]	-1.4 (0.68)	-2.8, -0.1	0.037*
Brief Pain Inventory SF Score[3]	-1.14 (0.215)	-1.56, -0.71	<0.001***

Baseline NPRS score is the mean of at least 5 days and no more than 7 days of scores from the Screening visit until treatment randomization. For the current pain baseline is the last score prior to treatment.

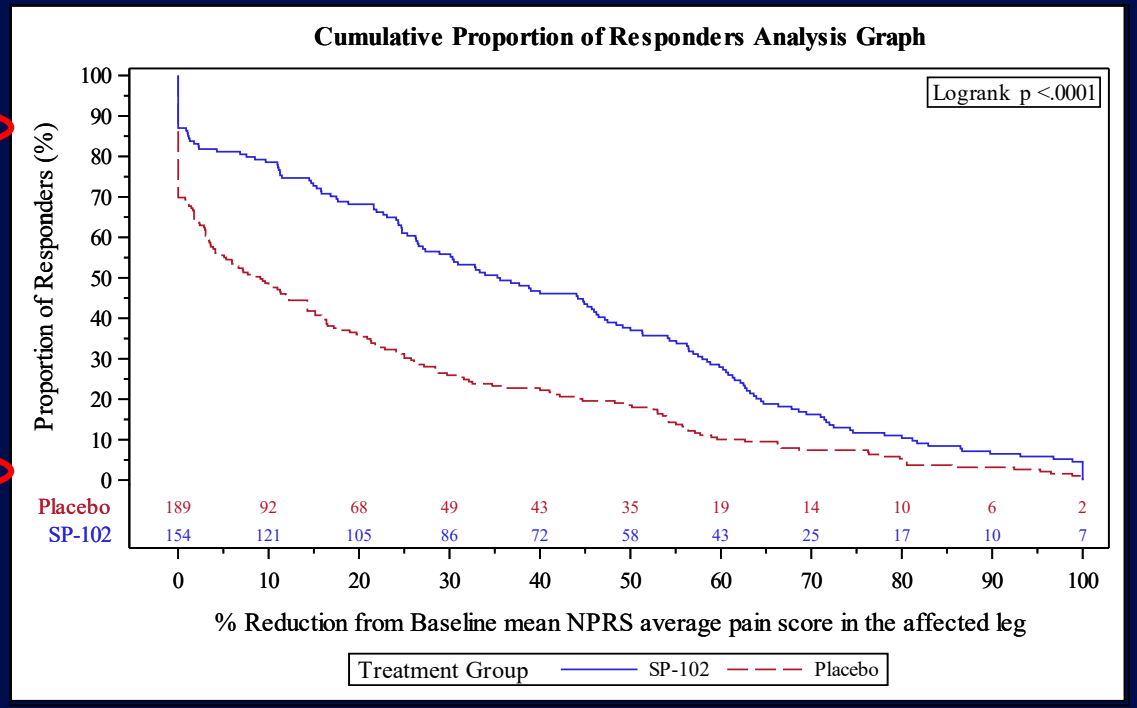
[1]The analysis uses a restricted maximum likelihood (REML) based mixed model for repeated measures (MMRM) with fixed effects for treatment (SP-102 or placebo), week, site, Pain Catastrophizing Scale group (<30 or ≥30), baseline averaged daily leg worst pain score, and treatment-by-week interaction. Tables 14.2.7.1, 14.2.8.1, 14.2.13.1

[2]The analysis uses an analysis of covariance (ANCOVA) model with fixed effects for treatment (SP-102 or placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline PainDETECT total score. Table 14.2.10.1.

[3]The analysis uses an analysis of covariance (ANCOVA) model with fixed effects for treatment (SP-102, Placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline BPI-SF score. Table 14.2.11.1.

Responder Analysis

Change from baseline in Mean NPRS, Average Daily Pain in Affected Leg	SP-102 N= 154	Placebo N=189
30% Reduction	**86 (55.8%)**	**49 (25.9%)**
Chi-Square: p-value <0.001***		
Logistic Regression: Odds Ratio (95% CI) - 3.91 (2.44, 6.28) p-value <0.001***		
50% Reduction	**58 (37.7%)**	**35 (18.5%)**
Chi-Square: p-value <0.001***		
Logistic Regression: Odds Ratio (95% CI) - 2.88 (1.74, 4.79) p-value <0.001***		
75% Reduction	**18 (11.7%)**	**14 (7.4%)**
Chi-Square: p-value 0.175		
Logistic Regression: Odds Ratio (95% CI) - 1.73 (0.81, 3.69) p-value 0.156		



Subjects that discontinued or have missing scores at Week 4 were considered non-responders. Logistic regression models with treatment (SP-102 or placebo), site, Pain Catastrophizing Scale group (<30 or ≥30), and baseline averaged daily leg pain score as factors were used to compare the treatment groups. Table 14.2.12.1. Figure 15.2.1

Proportion of Subjects Achieving a Response of 30% Reductions from Baseline in NPRS Average Pain Score in the Affected Leg @ Week 4 and NNT (Number Needed to Treat)

Visit	Statistic	SP-102 (N=154)		Placebo (N=189)
Week 4				
30% Reduction				
Number of Subjects with 30% Reduction	n (%)	86 **(55.8)**		49 **(25.9)**
Number of Subjects without 30% Reduction	n (%)	68 (44.2)		140 (74.1)
Chi-Square: Compare vs Placebo	p-value	<0.001***		
Logistic Regression: Compare vs Placebo	Odds Ratio (95% CI)	3.91 (2.44, 6.28)		
	p-value	<0.001***		
Number needed to treat		**3.3**		

Proportion of Subjects Achieving a Response of 50% Reductions from Baseline in NPRS Average Pain Score in the Affected Leg @ Week 4 and NNT (Number Needed to Treat)

Visit	Statistic	SP-102 (N=154)		Placebo (N=189)
Week 4				
50% Reduction				
Number of Subjects with 50% Reduction	n (%)	58 **(37.7)**		35 **(18.5)**
Number of Subjects without 50% Reduction	n (%)	96 (62.3)		154 (81.5)
Chi-Square: Compare vs Placebo	p-value	<0.001***		
Logistic Regression: Compare vs Placebo	Odds Ratio (95% CI)	2.88 (1.74, 4.79)		
	p-value	<0.001***		
Number needed to treat		**5.2**		

Hierarchical Arrangement of Endpoints

Sequential testing procedure. No alpha adjustments. All tests performed at the 0.05 level.	Statistically Significant Result
1. Mean change from Baseline to Week 4 in the mean NPRS average pain score in the affected leg. (Primary Efficacy Endpoint)	√
2. The change in ODI total score from Baseline to Week 4. (Key Secondary Endpoint)	√
3. PGIC	√
4. The time to repeat injection of SP-102 from index injection.	√
5. Proportion of subjects receiving repeat injection.	√
6. Mean Worst Pain in the affected leg	√
7. Mean Current Pain in the affected leg	√
8. Pain DETECT	√
9. Brief Pain Inventory - SF	√
10. Proportion of subjects achieving a response of 30%, 50%, and 75%	√ (not for 75%)
11. Mean Average Pain in lower back	√
12. CGIC	√
13. Cumulative use of rescue medication (mg of acetaminophen).	√
14. Time to first rescue medication dose	-
15. Proportion of subjects requiring rescue medications.	-

Safety Summary

- No AEs of special interest (paraplegia, hematoma, infection)
- No SAEs related to drug or injection procedure
- No meaningful differences in physical examinations, vital signs, or laboratory parameters between treatment groups

TEAEs Prior to Second Injection	SP-102 (N=202) Subjects n (%)	SP-102 (N=202) Events n	Placebo (N=199) Subjects n (%)	Placebo (N=199) Events n
Any TEAE	60 (**29.7**)	104	42 (**21.1**)	68
TEAE with >2% Incidence				
Headache	13 (6.4)	17	11 (5.5)	11
Injection site pain	4 (2.0)	4	0	0
Upper respiratory tract infection	2 (1.0)	2	4 (2.0)	4
Hypertension	4 (2.0)	4	1 (0.5)	2

Conclusions and Summary

- ✓ This is the largest prospective, R, DB, placebo-controlled study testing the effect and safety of a corticosteroid
- ✓ SP-102 showed meaningful pain relief with significantly large differences relative to placebo ($p < 0.001$) for the primary and almost all secondary pain and QOL endpoints over the 4-week primary analysis period
- ✓ SP-102 treatment arm demonstrated significantly longer time to repeat injection (median 99 days) compared to placebo (median 57 days)
- ✓ Study also demonstrated SP-102 administration having a safety profile with sparse AEs associated with SP-102 administration
- ✓ Data from the CLEAR Trial showed that SP-102 (dexamethasone viscous gel) is a safe and effective ESI in the treatment of lumbosacral radiculopathy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Thank you!!!