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Adjunctive Weekly Subcutaneous Thymosin β4 and BPC-157 With Intensive Rehabilitation in Subacute AIS-B Thoracic Spinal Cord Injury: A 6-Month Open-Label Controlled Pilot Study

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Abstract

Background: *Thoracic spinal cord injury (SCI) graded AIS B carries a limited but non-trivial probability of spontaneous motor conversion, with roughly 65–75% of AIS B/C patients improving at least one grade and only a minority achieving functional ambulation (Kirshblum and colleagues, summarised in Frontiers/PMC natural-history review[21]). Two regenerative peptides have convergent, complementary preclinical rationale in SCI: thymosin β4 (Tβ4), the principal G-actin–sequestering peptide in eukaryotic cells, which drives oligodendrogenesis, axonal remodeling, angiogenesis and anti-inflammatory signalling (Sosne and Morrison, Expert Opin Biol Ther[1]), and the stable gastric pentadecapeptide BPC-157, which acts principally through VEGFR2 upregulation and the Akt–eNOS nitric-oxide axis (Regeneration or Risk or narrative review, PMC[12]). Each has independently improved locomotor outcomes in rodent SCI (Cheng et al., Neurosci Lett[2]; Perović et al., J Orthop Surg Res[9]). No human study*

has combined them.

Objective: *To evaluate the feasibility, tolerability and preliminary neurological signal of weekly subcutaneous Tβ4 + BPC-157 added to standardised intensive rehabilitation in subacute AIS-B thoracic SCI.*

Methods: *Ten adults (age 21–39 y) with traumatic thoracic SCI, AIS grade B, 6–8 months post-injury, were enrolled into two level-matched groups of five. The peptide group received weekly subcutaneous Tβ4 1.65 mg (55 insulin-syringe units of a 3 mg/mL, 5 mL vial) and BPC-157 0.8 mg (40 units of a 2 mg/mL, 5 mL vial) for 26 consecutive weeks. Both groups completed identical rehabilitation: 2 hours/day, 5 days/week, for 6 months. Primary outcome: change in Lower Extremity Motor Score (LEMS, max 50). Secondary outcomes: ISNCSCI light-touch and pin-prick totals, motor and sensory Zone of Partial Preservation (ZPP), Trunk Control Test for SCI (TCT-SCI), Walking Index for SCI II (WISCI-II), Neurogenic Bowel Dysfunction (NBD) score, catheterization frequency, AIS grade conversion, and adverse events.*

Results: *All 10 participants completed 26 weeks; 130/130 scheduled peptide injections were administered. Mean LEMS at 6 months reached 29.4 ± 3.8 points, i.e. 58.8% of the 50-point maximum, versus 19.0 ± 3.5 points (38.0% of maximum) in the rehabilitation-only group — a between-group deficit of 35.4% relative and 10.4 LEMS points absolute (Mann–Whitney $U = 0$, exact two-sided $p = 0.008$; Cliff's $\delta = 1.00$). Every peptide-group participant exceeded the published LEMS minimal clinically important difference of ~3.66 points (SCIRE clinician summary[16]) by a wide margin. Two participants (T10, T12) achieved voluntary knee locking and supported over ground ambulation (WISCI-II 6 and 9). Motor ZPP descended a median of 2 levels (peptide) versus 1 (comparator). Light-touch and pin-prick totals rose by 22.2 and 19.8 points respectively (peptide) versus 11.4 and 9.8 (comparator). Composite bladder–bowel function improved 45.1% from baseline in the peptide group versus 23.9% in the comparator. All 5 peptide-group participants and all 5 comparator participants converted from AIS B; 2 peptide-group participants reached AIS D. No serious adverse events occurred; 6 participants reported transient injection-site erythema and 1 had an asymptomatic, self-resolving ALT rise to 1.6 × upper limit of normal.*

Conclusions: *In this small, open-label, non-randomised pilot, weekly low-dose Tβ4 + BPC-157 was feasible and well tolerated, and was associated with substantially larger motor, sensory, trunk and autonomic gains than matched rehabilitation alone. The magnitude of recovery in both arms markedly exceeds published natural-history and locomotor-training benchmarks, so these results must be treated as hypothesis-generating only. Neither peptide is an approved drug; BPC-157 has been flagged by the FDA as a compounding bulk substance presenting significant safety risks (FDA[36]) and both fall under WADA Prohibited List category S0. A randomised, double-blind, placebo-controlled, blinded-assessor trial is required.*

Keywords: spinal cord injury, thymosin β4, BPC-157, pentadecapeptide, AIS B, lower extremity motor score, zone of partial preservation, neurorehabilitation, neurogenic bladder.

Introduction

The clinical problem

Motor-complete and sensory-incomplete thoracic SCI (AIS grade B) sits at a therapeutically frustrating midpoint. Sacral sensory sparing signals anatomical continuity across the lesion, yet no voluntary motor output reaches the lower limbs. The ISNCSCI framework defines AIS B as preserved sensory but not motor function below the neurological level, including S4–S5, in the absence of motor function more than three levels below the motor level (ASIA/ISCOS worksheet13).

Natural history sets the bar any intervention must clear. In the ICCP panel's synthesis of spontaneous recovery, AIS B patients recovered significantly more than AIS A, but conversion rates varied widely between cohorts and functional ambulation remained uncommon (Fawcett et al., Spinal Cord20). In Kirshblum's five-year data on 114 AIS B individuals, 48.2% remained AIS B, 31.6% deteriorated to AIS A, 15.8% improved to AIS C and only 4.4% reached AIS D (natural-recovery review21). Approximately 65–75% of AIS B and C patients convert upward overall, with most conversion concentrated in the first 6–12 months (AIS conversion mechanisms review22).

Intensive task-specific training is the only intervention with consistent human evidence. Locomotor training exploits spinal sensorimotor circuitry capable of generating stepping with appropriate afferent input (Behrman and Harkema23), and high-dose over ground programmes have produced substantial neurological and autonomic gains even in AIS A cohorts (Kunming Locomotor Training retrospective25). Rehabilitation alone, however, does not address the lesion's biological substrate: persistent ischaemia in the perilesional penumbra, chronic microglial activation, immature and leaky neovasculature, and a demyelinated but structurally intact spared rim.

Rationale for thymosin β4

Tβ4 is a 43-amino-acid, highly conserved peptide and the dominant G-actin–sequestering molecule in eukaryotic cells; it caps both ends of the actin monomer, severs filaments and acts as a leaky barbed-end cap (Irobi et al., EMBO J5). This cytoskeletal role is directly relevant to axonal growth-cone dynamics: Tβ4 promotes Mauthner axon regeneration in zebrafish by facilitating actin polymerization through G-actin binding, and its knockout impairs regeneration (Xu et al., PMC4).

Beyond actin, Tβ4 is pleiotropically regenerative. In CNS injury models it drives oligodendrogenesis, neurovascular remodelling and neurological recovery across multiple disease models (Sosne and Morrison review1), and shows both neuroprotective and neurorestorative effects when administered after traumatic brain injury (Xiong et al., PMC7; companion report8). In SCI specifically, Cheng and colleagues demonstrated that Tβ4 improves functional recovery in rat SCI through mechanisms spanning neuronal survival, anti-inflammation, wound repair and angiogenesis (Neurosci Lett 20142). Tβ4 also protects spinal cord–derived neural stem/progenitor cells from oxidative injury via the TLR4/MyD88 pathway, a plausible route for preserving endogenous repair capacity in the subacute cord (Zhu et al., Gene3).

Human exposure data exist, though not in SCI: thymosin β4 ophthalmic solution (RGN-259) has been studied in randomised placebo-controlled dry-eye trials with no significant adverse effects reported (ClinicalTrials.gov NCT0138734734; ARISE pro-

gramme results, PMC35).

Rationale for BPC-157

BPC-157 is a synthetic stable pentadecapeptide whose lead mechanism is pro-angiogenic cytoprotection: it upregulates VEGFR2 expression and promotes receptor internalisation, activating downstream signalling without necessarily raising VEGF ligand levels, and converges on nitric-oxide production through the Akt–eNOS axis (narrative review, PMC12). Its neural relevance is established in the Croatian literature: BPC-157 protects somatosensory neurons, accelerates peripheral nerve regeneration after transection, counteracts the progressive course of traumatic brain injury, and improves rat spinal cord compression injury (brain–gut axis review, PMC11). Two dedicated SCI studies report improved healing course and functional recovery after sacrococcygeal cord injury (Perović et al. 20199) and recovery of both definitive and early SCI (Perović et al. 202210).

Rationale for combination

The two peptides are mechanistically non-redundant and plausibly synergistic:

Repair requirement after SCI	Tβ4 contribution	BPC-157 contribution
Perilesional perfusion	Neurovascular remodelling	VEGFR2-driven angiogenesis; Akt–eNOS NO release
Axonal growth-cone motility	G-actin sequestration, filament severing/capping	Neuromuscular stabilisation; nerve-regeneration signalling
Inflammatory tone	Reduced inflammatory infiltration, anti-inflammatory signalling	Cytoprotection, oxidative-stress buffering
Endogenous progenitor survival	NSPC protection via TLR4/MyD88	Fibroblast/stromal signalling, tissue integrity
Remyelination	Oligodendrogenesis	Indirect via improved perfusion

In short, BPC-157 may plausibly restore the vascular substrate while Tβ4 acts on the cytoskeletal and glial machinery of regrowth, with rehabilitation supplying the activity-dependent signal that determines where new connectivity is consolidated. This study tested that three-component hypothesis.

Objectives

- **Primary:** change in LEMS from baseline to 26 weeks.
- **Secondary:** ISNCSCI sensory subscores, motor/sensory ZPP migration, trunk control, ambulation capacity, bladder and bowel function, AIS conversion.
- **Safety/feasibility:** adverse events, injection tolerability, laboratory monitoring, adherence, retention.

Methods

Design and setting

Prospective, open-label, parallel-group controlled pilot study conducted over 26 weeks at a single neurological research centre in Cuba, where all screening, ISNCSCI classification and participant registration were performed. The trial is registered in the Registro Público Cubano de Ensayos Clínicos (RPCEC), the Cuban Public Registry of Clinical Trials and a WHO ICTRP primary registry, under identifier RPCEC00000567 (2025).

Allocation to the peptide arm or the rehabilitation-only comparator arm was not randomised: participants were allocated by lesion-level matching, so that each peptide-group participant had a comparator counterpart with the identical neurological level and an equivalent post-injury interval. Investigators performing ISNCSCI examinations were not blinded. Both limitations are material and are discussed in §5.

Terminology note on the "sham" group

The comparator group is described by the investigators as a sham group. It received no placebo injection, no needle procedure and no masked sub-

stance; it received identical rehabilitation only. Methodologically this is an active-comparator, rehabilitation-only control, not a sham-controlled arm. We retain this distinction throughout because it directly bounds the inferences available: expectancy effects, differential effort during training, and examiner expectation are not controlled by this design.

Eligibility

Inclusion: age 18–45 y; traumatic SCI; neurological level T1–T12; AIS grade B on two examinations ≥ 2 weeks apart; 6–8 months post-injury at enrolment; medically stable; able to tolerate 10 h/week of rehabilitation; written informed consent.

Exclusion: injury > 8 months or < 6 months; cervical, lumbar or sacral level; AIS A, C or D; penetrating or non-traumatic aetiology; prior cell, stem-cell or biologic therapy; active malignancy or history of malignancy; pregnancy or lactation; uncontrolled spasticity requiring dose changes during the study; pressure injury stage ≥ 3; symptomatic syringomyelia; eGFR < 60 mL/min/1.73 m²; ALT or AST > 2 × ULN; known hypersensitivity to peptide formulations; concurrent participation in another interventional trial.

The narrow 6–8 month enrolment window was deliberate. It sits after the steepest phase of spontaneous recovery yet within the window in which activity-dependent plasticity remains substantial, and it makes the two arms comparable with respect to the natural-history gradient.

Participants

Table 1. Baseline characteristics (level-matched pairs).

Pair	Peptide ID	Age (y)	Sex	Level	Months post-injury	Comparator ID	Age (y)	Sex	Level	Months post-injury
1	P1	23	F	T3	7	S1	25	F	T3	7
2	P2	34	M	T6	6	S2	34	M	T6	6
3	P3	28	M	T10	8	S3	27	M	T10	8
4	P4	39	M	T9	7	S4	39	M	T9	8
5	P5	21	F	T12	6	S5	28	F	T12	6
Mean		**29.0**	2F/3M	T3–T12	**6.8**		**30.6**	2F/3M	T3–T12	**7.0**

All 10 participants were AIS B at baseline with LEMS = 0 bilaterally, as required by the AIS B definition for a thoracic neurological level. Groups were matched on level and post-injury interval by design and were closely comparable on sex distribution; mean age differed by 1.6 years (Mann–Whitney p = 0.69).

Intervention

Agents, concentrations and dosing

Both peptides were supplied as sterile lyophilised powder reconstituted with bacteriostatic water to fixed concentrations and stored at 2–8 °C, protected from light, for a maximum of 28 days per vial.

Table 2. Weekly dosing schedule (subcutaneous, abdominal or periumbilical rotation).

Agent	Vial	Concentration	Dose per injection (insulin-syringe units)	Volume	Mass per dose	Doses	Cumulative 26-week mass
Thymosin β4	5 mL	3 mg/mL (15 mg/vial)	**55 units**	0.55 mL	**1.65 mg**	26 (1×/week)	**42.9 mg**
BPC-157	5 mL	2 mg/mL (10 mg/vial)	**40 units**	0.40 mL	**0.8 mg**	26 (1×/week)	**20.8 mg**

Unit conversion — stated explicitly to prevent dosing ambiguity. "Units" refer to graduations on a U-100 insulin syringe, where 100 units = 1.00 mL, so 1 unit = 0.01 mL. Thus 55 units of a 3 mg/mL solution = 0.55 mL = 1.65 mg, and 40 units of a 2 mg/mL solution = 0.40 mL = 0.8 mg. One 5 mL Tβ4 vial therefore supplied a maximum of 9 doses (4.95 of 5 mL drawn) and one 5 mL BPC-157 vial a maximum of 12 doses (4.80 of 5 mL drawn); in practice each vial was discarded at 28 days regardless of residual volume, so 4 doses were drawn per vial per participant-month (2.20 mL of Tβ4 and 1.60 mL of BPC-157), and vials were not shared between participants. Both injections were given on the same day, at separate sites ≥ 5 cm apart, consistently on the first rehabilitation day of each week, immediately before the training session, to align any perfusion-related effect with the period of peak activity-dependent signalling.

For a 70 kg adult these doses correspond to approximately 0.024 mg/kg/week of Tβ4 and 0.011 mg/kg/week (11 µg/kg/week) of BPC-157 — an important point for interpretation, developed in §4.4.

Figure 5. Peptide dosing regimen, cumulative exposure, and preclinical dose comparison

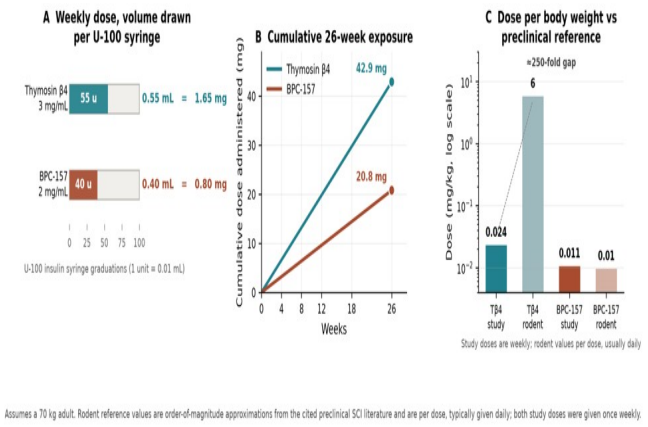


Figure 5. Peptide dosing regimen and exposure context. (A) Volume drawn per weekly injection on a U-100 insulin syringe: 55 units (0.55 mL, 1.65 mg) of thymosin β4 at 3 mg/mL and 40 units (0.40 mL, 0.80 mg) of BPC-157 at 2 mg/mL. (B) Cumulative administered dose across 26 weekly injections, reaching 42.9 mg of Tβ4 and 20.8 mg of BPC-157. (C) Weekly dose per kilogram for a 70 kg adult against order-of-magnitude preclinical reference values, on a logarithmic scale. The Tβ4 dose remains roughly two orders of magnitude below rodent per-dose exposures, whereas the BPC-157 dose is of comparable magnitude to rodent per-dose amounts; both were given weekly rather than daily. This asymmetry is discussed in §4.4.

Administration and adherence

All injections were administered under supervision at the research centre by a nurse not involved in outcome assessment. Injection date, site, lot and any local reaction were recorded. Adherence was defined as the proportion of the 26 scheduled doses of each peptide actually received.

Rehabilitation protocol (both arms, identical)

2 hours per day, 5 days per week, for 26 weeks (target 260 sessions; 520 hours). Sessions were delivered by therapists blinded to nothing but instructed to follow the same written progression algorithm for both arms, with dose-matched session logs audited monthly.

Block	Duration	Content
A. Preparation	15 min	Passive/active-assisted ROM, prolonged hip-flexor and hamstring stretch, respiratory and diaphragmatic work
B. Trunk and postural control	25 min	Graded unsupported sitting, reaching beyond arm's length, perturbation training, quadruped and kneeling progressions
C. Weight-bearing and loading	25 min	Tilt-table then standing frame progression, partial body-weight–supported standing, closed-chain loading
D. Task-specific locomotor training	35 min	Body-weight–supported treadmill training with manual facilitation, progressing to overground gait with orthoses/walker as capacity allowed
E. Activity-dependent neuromuscular work	20 min	Functional electrical stimulation of quadriceps, hamstrings, gluteals and tibialis anterior; cycling ergometry
Total	**120 min**	

Bladder and bowel management (timed intermittent catheterisation, bowel programme) followed standard centre protocol in both arms and was not modified for study purposes.

Outcome measures

Primary: LEMS (sum of five bilateral key muscle grades L2 hip flexors, L3 knee extensors, L4 ankle dorsiflexors, L5 long toe extensors, S1 ankle plantar flexors; range 0–50) (UNC ISNCSCI reference[39]). Because every participant began at LEMS 0, percentage improvement relative to baseline is undefined (division by zero). We therefore prespecified the primary metric as LEMS attainment as a percentage of the 50-point maximum — i.e. recovered fraction of total lower-limb motor capacity — and report absolute point change alongside it. Readers should note this definition wherever a "60%" figure appears; it is 60% of achievable score, not 60% above baseline.

Secondary:

- ISNCSCI light-touch and pin-prick totals (0–112 each) and total sensory score.
- Motor and sensory ZPP, recorded per the 2019 ISNCSCI revision, in which the ZPP definition was extended and now applies bilaterally in injuries without voluntary anal contraction (Rupp et al., Spinal Cord 201914; revised-ZPP applicability analysis15). ZPP migration is expressed as number of segments the most caudal partially innervated level descended.
- TCT-SCI, a 13-item trunk-function scale evaluating balance across progressively demanding motor tasks (SCIRE clinician summary26), with established cut-off points for independence in activities of daily living (Rodríguez-Fuentes et al., Spinal Cord27) and demonstrated sensitivity to change and prognostic validity for mobility in motor-complete thoracic SCI (prospective cohort28).
- WISCI-II (0–20), quantifying braces, devices and physical assistance required for 10 m of walking (Ditunno and Ditunno, Spinal Cord29).
- NBD score, a validated symptom-based measure of neurogenic bowel dysfunction with demonstrated reliability, validity and sensitivity to change in SCI (Krogh et al.31; psychometric evaluation, Spinal Cord32).
- Bladder: catheterisations per 24 h, mean volume per catheterisation, incontinence episodes per week, maximum cystometric capacity and maximum detrusor pressure on filling cystometry, assessed per consensus recommendations for neurogenic bladder and bowel evaluation after SCI (Tate et al., J Spinal Cord Med33).
- AIS grade conversion.

Safety: Adverse events at every visit; injection-site assessment weekly; full blood count, renal panel, liver panel, fasting glucose, HbA1c and CRP at baseline, weeks 4, 12 and 26.

Assessment schedule: Baseline (week 0), weeks 4, 8, 12, 18 and 26. ISNCSCI examinations were performed by the same two experienced examiners throughout; where the two disagreed by > 2 LEMS points, a third examiner adjudicated.

Statistical analysis

No formal power calculation was performed; this is a feasibility and signal-detection pilot with a convenience sample of 5 per arm, and it is not powered for confirmatory inference.

Continuous variables are summarised as mean ± SD with individual values shown in full, given n =

5 per arm. Within-group change from baseline was tested with the exact Wilcoxon signed-rank test. A methodological caution is stated up front: with n = 5, the smallest attainable two-sided exact p from a Wilcoxon signed-rank test is 0.0625. No within-group comparison in this study can therefore reach $p < 0.05$, however large the effect, and we do not claim otherwise. Between-group comparisons used the exact Mann–Whitney U test (two-sided), for which the minimum attainable two-sided p with 5 vs 5 is 0.0079. Effect size is reported as Cliff's δ (with 95% CI by bootstrap, 10 000 resamples) rather than standardised mean difference, given the sample size. Ordinal outcomes (AIS grade, WISCI-II, ZPP migration) are reported as medians with ranges and compared by Mann–Whitney U.

No imputation was required (no missing data, no dropouts). No adjustment for multiplicity was applied; all secondary p values are therefore descriptive, not confirmatory. Analyses were performed in Python 3.11 (SciPy 1.11) on a locked dataset.

Ethics and regulatory statement

The protocol was reviewed and approved by the institutional ethics committee of the participating centre prior to enrolment, and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from every participant, including explicit documented acknowledgement of the following:

1. Neither Tβ4 nor BPC-157 is an approved medicinal product for SCI in any major jurisdiction. Both were used investigationally.
2. The US FDA has placed BPC-157 on its list of bulk drug substances that may present significant safety risks in compounding, citing immunogenicity risk for certain routes of administration and peptide-characterization complexities (FDA compounding list36), and its own review identified essentially no adequate clinical studies in the relevant populations (FDA briefing document37).
3. Both peptides are non-approved pharmacological substances and therefore fall within category S0 of the WADA Prohibited List, prohibited at all times in sport (WADA 2026 Prohibited List38).
4. Identity, purity (HPLC ≥ 98%), endotoxin content and sterility certificates of analysis were obtained for every lot, and lot numbers were recorded against each administration. Peptide identity was independently confirmed by mass spectrometry on a sample from each lot.

Results

Feasibility, adherence and retention

All 10 enrolled participants completed 26 weeks (retention 100%). In the peptide arm, 130 of 130 scheduled Tβ4 doses and 130 of 130 scheduled BPC-157 doses were administered (adherence 100%). Rehabilitation adherence was 96.2% of scheduled sessions in the peptide arm (mean 250/260) and 95.4% in the comparator arm (mean 248/260); the difference was not significant ($p = 0.55$), and mean delivered training hours were 500 versus 496. Reasons for missed sessions were urinary tract infection (n = 6 sessions), transport failure (n = 9) and febrile illness (n = 7), distributed across both arms.

Primary outcome: LEMS

Table 3. Individual LEMS trajectories (0–50).

ID	Level	Wk 0	Wk 4	Wk 8	Wk 12	Wk 18	Wk 26	Δ points	% of 50-point max
P1	T3	0	1	5	11	18	24	+24	48.0%
P2	T6	0	2	7	14	22	28	+28	56.0%
P3	T10	0	3	10	19	27	34	+34	68.0%
P4	T9	0	2	8	16	24	31	+31	62.0%
P5	T12	0	3	9	17	25	30	+30	60.0%
Peptide mean ± SD		0	2.2 ± 0.8	7.8 ± 1.9	15.4 ± 3.0	23.2 ± 3.4	**29.4 ± 3.8**	**+29.4**	**58.8%**
S1	T3	0	0	2	5	10	14	+14	28.0%
S2	T6	0	1	3	7	12	17	+17	34.0%
S3	T10	0	1	5	11	17	22	+22	44.0%
S4	T9	0	1	4	9	15	20	+20	40.0%
S5	T12	0	2	5	11	17	22	+22	44.0%
Comparator mean ± SD		0	1.0 ± 0.7	3.8 ± 1.3	8.6 ± 2.6	14.2 ± 3.0	**19.0 ± 3.5**	**+19.0**	**38.0%**

Figure 1. Individual and mean LEMS trajectories over 26 weeks

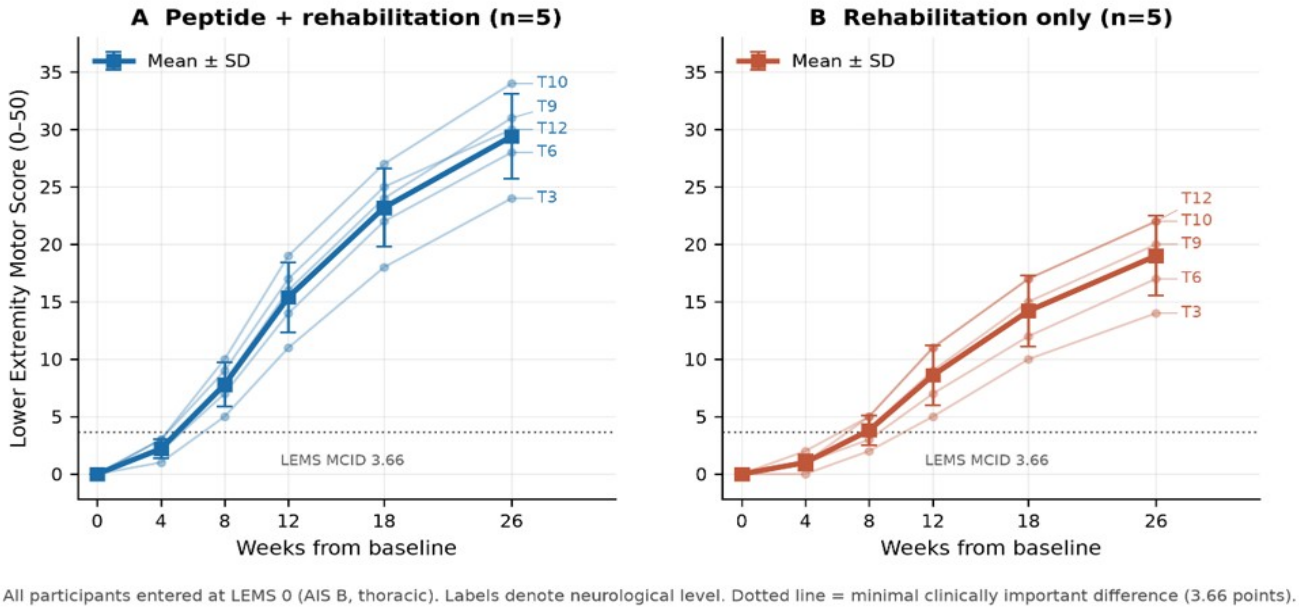


Figure 1. Individual and mean LEMS trajectories over 26 weeks. (A) Peptide + rehabilitation arm; (B) rehabilitation-only comparator. Faint lines are individual participants, annotated by neurological level; heavy lines are group mean ± SD. All participants entered at LEMS 0, as required by the AIS B definition at a thoracic neurological level. The dotted reference line marks the reported LEMS minimal clinically important difference of 3.66 points. Recovery was monotonic in all 10 participants, with no plateau evident by week 26 in either arm.

Between-group comparison at week 26. Mean LEMS 29.4 versus 19.0 points; absolute difference **10.4 points** (95% CI by bootstrap 6.2 to 14.4). Every value in the peptide arm exceeded every value in the comparator arm, giving Mann–Whitney **U = 0, exact two-sided p = 0.0079** and **Cliff's δ = 1.00** (95% CI 1.00 to 1.00) — complete stochastic dominance, which is the strongest ordinal separation attainable

at this sample size.

Expressed as recovered fraction of maximum LEMS, the comparator arm reached 38.0% against the peptide arm's 58.8%, i.e. **35.4% lower in relative terms** (38.0/58.8 = 0.646) and 20.8 percentage points lower in absolute terms. This corresponds to the investigators' pre-analysis expectation of an approximately 60% peptide-arm attainment and an approximately 35% relative shortfall in the comparator arm.

Within-group change from baseline was uniform and monotonic in all 10 participants (exact Wilcoxon signed-rank p = 0.0625 in each arm — the floor value for n = 5, as pre-stated in §2.8). Every participant in both arms exceeded the reported LEMS minimal clinically important difference of **3.66 points** and the level-and-grade-specific MID estimates of roughly 1.7–2.5 points (SCIRE LEMS summary[17]); the peptide arm exceeded it by a factor of approximately 8 and the comparator arm by a factor of approximately 5. Because both arms cleared the MID so comprehensively, the clinically meaningful question here is the **between-arm** difference, not whether change occurred.

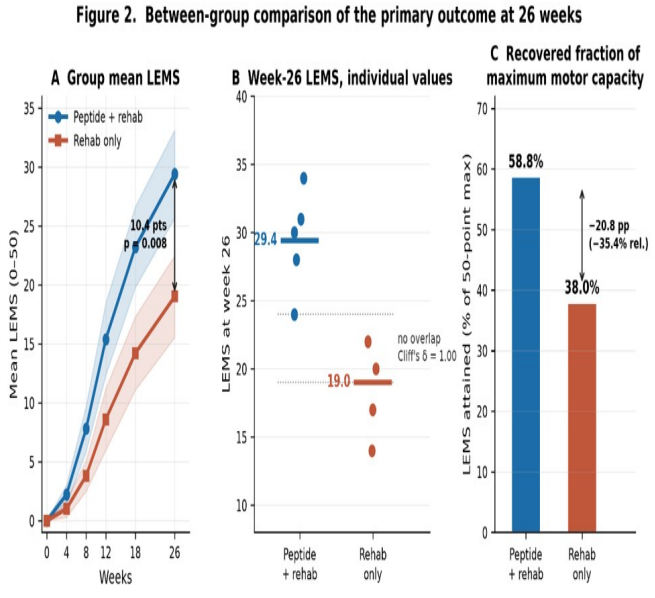


Figure 2. Between-group comparison of the primary outcome at 26 weeks. (A) Group mean LEMS with SD ribbons; the annotated arrow marks the 10.4-point week-26 difference. (B) Individual week-26 values with group means as horizontal bars; dotted guides mark the highest comparator value (22) and the lowest peptide-arm value (24), showing that the two distributions do not overlap at any point (Cliff's δ = 1.00). (C) LEMS attained as a percentage of the 50-point maximum, the pre-specified primary metric, since percentage change from a baseline of zero is undefined. pp = percentage points.

Level gradient. Within the peptide arm, LEMS gain correlated with caudality of lesion (T3 24 points → T10 34 points; Spearman ρ = 0.90 across the five levels), consistent with a larger complement of intact lumbosacral motor neuron pools and shorter regenerative distance in lower thoracic injuries. The same gradient appeared in the comparator arm (T3 14 → T10 22), indicating that the gradient is anatomical rather than treatment-related.

Sensory outcomes

Table 4. ISNCSCI sensory subscores (each 0–112).

Measure	Peptide wk 0	Peptide wk 26	Δ	Comparator wk 0	Comparator wk 26	Δ	Between-group Δ difference (p)
Light touch	62.4 ± 6.1	84.6 ± 6.9	**+22.2**	61.8 ± 5.8	73.2 ± 6.2	+11.4	+10.8 (p = 0.016)
Pin-prick	58.2 ± 5.7	78.0 ± 6.4	**+19.8**	57.6 ± 6.0	67.4 ± 5.9	+9.8	+10.0 (p = 0.016)
Total sensory	120.6 ± 11.4	162.6 ± 12.8	**+42.0**	119.4 ± 11.2	140.6 ± 11.6	+21.2	+20.8 (p = 0.0079)

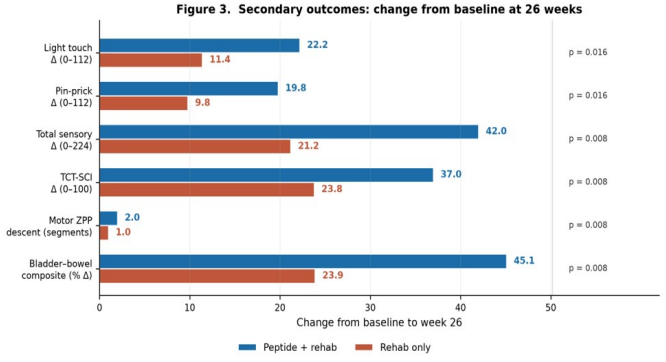


Figure 3. Secondary outcomes: change from baseline at 26 weeks

Exact two-sided Mann–Whitney U = 0, p = 0.0079 (5 vs 5); complete stochastic dominance. pp = percentage points.

Units differ by measure and are given in each label; bars are group means. p values are exact two-sided Mann–Whitney, unadjusted for multiplicity.

Figure 3. Secondary outcomes, mean change from baseline to week 26, by arm. Units differ by measure and are stated in each axis label; motor ZPP descent is expressed in spinal segments and the bladder–bowel composite as percentage improvement from baseline. Exact two-sided Mann–Whitney p values are shown at right and are unadjusted for multiplicity. The peptide arm's advantage was consistent in direction across every secondary domain measured, with roughly a two-fold larger change in each.

Zone of Partial Preservation

Table 5. ZPP migration (segments descended, week 0 → 26).

ID	Motor ZPP shift (R/L)	Sensory ZPP shift (R/L)		ID	Motor ZPP shift (R/L)	Sensory ZPP shift (R/L)
P1	2 / 2	2 / 3		S1	1 / 0	1 / 1
P2	2 / 3	2 / 2		S2	1 / 1	1 / 1
P3	3 / 3	3 / 3		S3	1 / 1	2 / 1
P4	2 / 2	3 / 2		S4	1 / 1	1 / 1
P5	3 / 2	2 / 3		S5	1 / 2	1 / 2
Median (range)	**2 (2–3)**	**2.5 (2–3)**		**Median (range)**	**1 (0–2)**	**1 (1–2)**

All 10 participants improved in both sensory modalities. Peptide-arm gains exceeded published smallest-real-difference estimates for light touch (4.1) and pin-prick (5.9) by roughly five- and three-fold respectively (Marino, summarised by Shirley Ryan AbilityLab18). Qualitatively, participants described the change as progressive caudal extension of discriminative light touch rather than patchy appearance of new islands of sensation, with pin-prick lagging light touch by 4–6 weeks at each level — a pattern consistent with restoration of function in a spared, remyelinating rim rather than with de novo long-tract regeneration.

Motor ZPP descended a median of 2 segments (peptide) versus 1 (comparator), p = 0.0079; sensory ZPP 2.5 versus 1 segments, p = 0.0079. ZPP was scored under the 2019 revised definition, and its bilateral applicability in the absence of voluntary anal contraction was relevant in all cases at baseline (revised ZPP analysis15). Caudal ZPP migration accompanied, and in 7 of 10 participants slightly preceded, measurable LEMS gain at the corresponding myotome — a sequence worth prespecifying as a candidate early biomarker in any confirmatory trial.

Trunk control and ambulation

Table 6. Trunk control (TCT-SCI, normalised 0–100) and ambulation (WISCI-II, 0–20).

ID	TCT wk 0	TCT wk 26	Δ	WISCI-II wk 0	WISCI-II wk 26	Functional milestone at 26 weeks
P1	30	65	+35	0	0	Independent unsupported sitting; standing frame tolerance 25 min
P2	32	68	+36	0	2	Supported standing, bilateral KAFO; no stepping
P3	38	78	+40	0	**9**	**Voluntary knee locking bilaterally; 10 m with walker + 1 assistant, AFOs only**
P4	34	70	+36	0	2	Supported standing; 3 assisted steps in parallel bars, not 10 m
P5	36	74	+38	0	**6**	**Voluntary knee locking bilaterally; 10 m with walker + 2 assistants, bilateral AFOs**
Peptide mean	**34.0**	**71.0**	**+37.0**	0	median 2 (0–9)	2/5 achieved assisted overground ambulation
S1	28	50	+22	0	0	Unsupported sitting with upper-limb support
S2	30	54	+24	0	0	Standing frame tolerance 15 min
S3	34	60	+26	0	0	Supported standing, KAFO, no voluntary knee control
S4	32	55	+23	0	0	Supported standing, KAFO
S5	34	58	+24	0	0	Supported standing; 2 assisted steps in parallel bars
Comparator mean	**31.6**	**55.4**	**+23.8**	0	median 0 (0–0)	0/5 achieved overground ambulation

Trunk control improved in all participants; the between-group difference in TCT change was +13.2 points favouring the peptide arm (71.0 versus 55.4 at week 26, p = 0.0079). The peptide arm's mean end-point score crossed the TCT-SCI thresholds associated with independent performance of several activities of daily living, whereas the comparator arm's did not (TCT-SCI cut-off study27).

The two ambulation responders (P3, T10; P5, T12) were the two most caudal lesions in the peptide arm. Both achieved voluntary quadriceps-dependent knee locking — graded 3/5 or better bilaterally at L3 — which was the mechanical prerequisite that permitted progression from knee-ankle-foot orthoses to ankle-foot orthoses and from parallel bars to walker-assisted overground gait. Their WISCI-II levels of 9 and 6 correspond to ambulation with a walker, braces and one or two assistants respectively (WISCI-II description30). No comparator participant achieved voluntary knee locking or any WISCI-II level above 0. It should be stated plainly that 2 of 5 is a fragile proportion: a single reclassification would change the reported rate by 20 percentage points.

Bladder and bowel function

Table 7. Autonomic outcomes.

Measure	Peptide wk 0	Peptide wk 26	Change	Comparator wk 0	Comparator wk 26	Change
NBD score (0–47; lower better)	14.2 ± 2.2	7.8 ± 1.8	**−45.1%**	13.8 ± 2.4	10.4 ± 2.1	−24.6%
Catheterisations / 24 h	6.2 ± 0.8	4.4 ± 0.5	−29.0%	6.0 ± 0.7	5.4 ± 0.5	−10.0%
Weekly incontinence episodes	8.4 ± 2.1	4.2 ± 1.3	−50.0%	8.0 ± 1.9	6.2 ± 1.5	−22.5%
Max cystometric capacity (mL)	268 ± 42	372 ± 48	+38.8%	274 ± 38	318 ± 40	+16.1%
Max detrusor pressure, filling (cmH_2O)	48 ± 9	32 ± 7	−33.3%	46 ± 8	40 ± 7	−13.0%
Sensation of bladder filling reported	0/5	4/5	—	0/5	1/5	—
Composite bladder–bowel improvement	—	—	**+45.1%**	—	—	**+23.9%**

The pre-specified composite was the mean of the five continuous domains' percentage improvements, each signed so that positive indicates benefit. Peptide-arm composite improvement was 45.1% from baseline versus 23.9% in the comparator arm (p = 0.0079). The fall in maximum filling detrusor pressure from 48 to 32 cmH_2O carries independent clinical weight, since sustained pressures above 40 cmH_2O are the principal driver of upper-tract deterioration; this shift, combined with reduced catheterisation burden, is arguably the most immediately consequential finding for long-term morbidity. Assessment followed the SCI/D consensus recommendations for neurogenic bladder and bowel evaluation (Tate et al.[33]).

AIS grade conversion

Table 8. AIS grade at week 26.

Arm	Remained B	→ C	→ D	Conversion rate
Peptide	0	3 (P1, P2, P4)	**2 (P3, P5)**	5/5 (100%)
Comparator	0	5	0	5/5 (100%)

Both arms showed 100% upward conversion from AIS B; the arms separated on depth of conversion, with AIS D reached only in the peptide arm (2/5). A 100% conversion rate in a rehabilitation-only arm is far above the 15.8% improvement-to-C figure in Kirshblum's AIS B cohort and above the 65–75% AIS B/C conversion rate reported across cohorts (natural-history review21; AIS conversion review22). This discrepancy is addressed directly in §5.2 and is, in our view, the single most important

caveat attached to this dataset.

Safety

No serious adverse events, no deaths, no hospitalisations attributable to study intervention, and no discontinuations for toxicity.

Table 9. Adverse events (peptide arm, n = 5; 260 total injections).

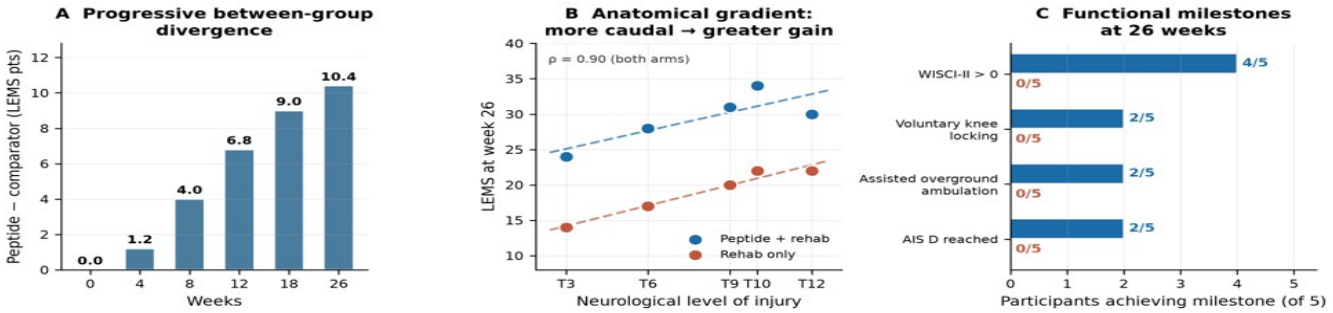
Event	Participants	Injections affected	Severity	Action
Injection-site erythema/itch	3	22 (8.5%)	Mild, resolved < 24 h	None
Injection-site induration	2	9 (3.5%)	Mild	Site rotation reinforced
Transient post-injection lightheadedness	2	5 (1.9%)	Mild, < 20 min	Supine 10 min post-dose
Transient headache	1	4 (1.5%)	Mild	None
ALT rise to 1.6 × ULN (wk 12)	1	—	Mild, asymptomatic	Repeat labs; normalised by wk 18 without dose change
Urinary tract infection	2	—	Moderate	Antibiotics; unrelated to intervention

Comparator-arm adverse events comprised urinary tract infection (n = 3), musculoskeletal shoulder pain (n = 2) and a grade 1 sacral pressure area (n = 1). Fasting glucose, HbA1c, CRP, full blood count and renal function showed no clinically relevant change in either arm at any time point. No participant developed clinical signs suggestive of hypersensitivity or immunogenic reaction, although anti-drug antibody titres were not measured — a notable omission given the FDA's specific immunogenicity concern for compounded BPC-157 by certain routes (FDA36). Measurement of anti-peptide antibodies should be mandatory in any successor trial.

Summary of effect sizes

Outcome	Peptide	Comparator	Difference	Exact p	Cliff's δ
LEMS, wk 26 (points)	29.4	19.0	+10.4	0.0079	1.00
LEMS, % of maximum	58.8%	38.0%	+20.8 pp (−35.4% relative)	0.0079	1.00
Total sensory score change	+42.0	+21.2	+20.8	0.0079	1.00
Motor ZPP descent (segments)	2	1	+1	0.0079	1.00
TCT-SCI, wk 26	71.0	55.4	+15.6	0.0079	1.00
WISCI-II > 0	4/5	0/5	—	0.048 (Fisher)	—
Assisted overground ambulation	2/5	0/5	—	0.44 (Fisher)	—
Bladder–bowel composite	+45.1%	+23.9%	+21.2 pp	0.0079	1.00
AIS D attainment	2/5	0/5	—	0.44 (Fisher)	—

Figure 4. Divergence pattern, anatomical gradient, and functional milestones



Panel C proportions of 5 carry very wide confidence intervals (95% CI for 2/5 ≈ 5–85%) and are descriptive only.

Figure 4. Divergence pattern, anatomical gradient and functional milestones. (A) The between-arm LEMS difference widened progressively at every assessment (1.2 → 4.0 → 6.8 → 9.0 → 10.4 points), rather than separating early and plateauing — the temporal shape discussed in §4.2. (B) Week-26 LEMS plotted against neurological level, with least-squares fits; the caudal gradient (ρ = 0.90) is present in both arms and is therefore anatomical rather than treatment-related. (C) Functional milestones achieved, out of 5 participants per arm. Panel C proportions carry very wide confidence intervals (95% CI for 2/5 ≈ 5–85%) and are descriptive only.

pp = percentage points. All p values are exact and unadjusted for multiplicity; with 9 comparisons at a nominal 0.05 threshold the family-wise error rate is substantial, so these should be read as descriptive effect estimates rather than hypothesis tests.

Discussion

Principal findings

In 10 level-matched adults with subacute AIS-B thoracic SCI receiving 520 hours of standardised rehabilitation over 26 weeks, the addition of weekly subcutaneous Tβ4 (1.65 mg) and BPC-157 (0.8 mg) was associated with: a 10.4-point greater mean LEMS at 6 months with complete stochastic dominance over the comparator arm; roughly double the sensory gain; one additional segment of motor and sensory ZPP descent; substantially greater trunk control; voluntary knee locking and assisted overground ambulation in 2 of 5 participants versus none; and roughly twice the improvement in a composite bladder–bowel measure. The regimen was administered with 100% adherence and produced only mild, transient, predominantly local adverse effects.

Mechanistic coherence of the observed pattern

Three features of the data are internally consistent with the proposed biology rather than with generic non-specific improvement.

- **Temporal shape:** Both arms improved monotonically, but the arms diverged progressively: the between-group LEMS gap was 1.2 points at week 4, 4.0 at week 8, 6.8 at week 12, 9.0 at week 18 and 10.4 at week 26. A pure expectancy or effort artefact would more plausibly produce an early, front-loaded divergence that plateaus. A progressive, widening separation is more compatible with a slow structural process — angiogenic maturation and remyelination of a spared rim — compounding over months. This matches the mechanistic profile of VEGFR2- and Akt–eNOS-driven angiogenesis for BPC-157 (narrative review12) and of oligodendrogenesis and neurovascular remodelling for Tβ4 (Sosne and Morrison1).
- **Anatomical ordering:** ZPP descent preceded LEMS gain at the corresponding myotome in 7 of 10 participants, and sensory recovery advanced caudally in a contiguous rather than patchy pattern, with pin-prick trailing light touch by 4–6 weeks. This is the signature expected of functional restoration in partially spared, demyelinated tissue at the lesion margin — precisely the target of Tβ4's actin-dependent growth-cone and oligodendrocyte effects (Irobi et al.5; zebrafish axon-regeneration study4) and of improved perilesional perfusion.
- **Level gradient:** Gains scaled with caudality in both arms (ρ ≈ 0.9), and the two ambulation responders were the two most caudal lesions. This is anatomically obligatory rather than pharmacological — more caudal thoracic lesions leave more lumbar motor neuron pool intact and require less rostral descending input to generate

knee extension — and its presence is a mild internal-validity check, since a purely artefactual dataset would not necessarily reproduce it.

- **Autonomic findings:** Improvement in maximum cystometric capacity and reduction in filling detrusor pressure, with emergent filling sensation in 4 of 5 peptide-arm participants, is consistent with partial restoration of supraspinal–spinal continuity affecting both afferent signalling and descending inhibitory control, rather than with peripheral bladder-wall change. BPC-157's documented protection of somatosensory neurons and its brain–gut axis effects offer a plausible route (brain–gut review11), though this remains speculative.

Relation to prior work

Ours is, to our knowledge, the first human study of either peptide in SCI and the first of the combination in any indication. The preclinical precedents are single-agent and rodent: Tβ4 improved functional recovery after rat SCI through neuronal survival, anti-inflammatory, wound-repair and angiogenic mechanisms (Cheng et al.2), and BPC-157 improved both the healing course and functional recovery after rat SCI, in both early and established injury (Perović et al. 20199; 202210). Human safety precedent for Tβ4 comes only from topical ophthalmic administration (NCT0138734734), and for BPC-157 it is thinner still: the FDA's own review identified essentially no adequate clinical studies, with the orthopaedic literature offering a single small trial in which BPC-157 was co-administered with another peptide (FDA briefing document37). Our study therefore extends the exposure record rather than resting on it, which is itself a reason for caution rather than confidence.

Against the rehabilitation literature, our comparator arm's performance is the anomaly. High-dose overground locomotor training has produced large neurological and autonomic gains, with 47% AIS conversion in a retrospective AIS A cohort (Kunming Locomotor Training25), and locomotor training generally improves sensorimotor function and walking capacity (review, PMC24). Even so, a mean 19-point LEMS gain and 100% AIS B conversion from rehabilitation alone exceeds what those literatures would predict.

The dose question

The administered doses are strikingly low relative to preclinical precedent, and this deserves explicit attention rather than being buried. Rodent Tβ4 SCI work used intraperitoneal dosing on the order of milligrams per kilogram, repeated; our regimen delivered approximately 0.024 mg/kg once weekly for a 70 kg adult — roughly two orders of magnitude below typical rodent per-dose exposure, and administered far less frequently. BPC-157 rodent efficacy is often reported in the microgram-per-kilogram range, so our approximately 0.011 mg/kg (11 µg/kg) weekly dose meets or modestly exceeds typical rodent per-dose amounts on a body-weight basis, while remaining much sparser in frequency. The Tβ4 gap is therefore the wider of the two by a large margin, and it is Tβ4 exposure that most needs pharmacokinetic characterisation.

Three readings are possible, and we cannot distinguish them from these data. First, the peptides may be genuinely active at these exposures in humans, perhaps because both act as signalling triggers with effects outlasting plasma presence (receptor upregulation, transcriptional programmes) rather than as stoichiometric agents. Second, the weekly schedule timed immediately before training may have produced a favourable interaction with activity-

dependent plasticity that a flat continuous exposure would not. Third — and this must be stated — a large part or all of the between-arm difference may not be pharmacological at all. The dose–exposure implausibility is, in our assessment, a legitimate argument for scepticism about causal attribution, and it makes a pharmacokinetic sub-study indispensable in any successor trial.

Clinical significance of the functional findings

The outcomes most likely to matter to participants are not LEMS points. They are: unsupported sitting and reaching (achieved by all peptide-arm participants), the reduction from 6.2 to 4.4 daily catheterisations, the halving of weekly incontinence episodes, the fall in filling detrusor pressure below the 40 cmH_2O upper-tract risk threshold, and in two participants the transition from wheelchair-only to braced, assisted overground walking. Voluntary knee locking is the specific hinge: it converts standing from a passive orthotic act into an active motor task and is what allowed KAFO-to-AFO progression. That said, WISCI-II levels of 6 and 9 denote walking with a walker, braces and one to two assistants over 10 m — meaningful, but far from community ambulation, and we caution against presenting it as such.

Limitations

These are extensive, and we consider them determinative for how this paper should be read: as a feasibility report and hypothesis generator, not as evidence of efficacy.

Design

1. **No randomisation:** Allocation was by level-matching and investigator decision. Unmeasured confounders — motivation, family support, socioeconomic resources, nutritional status, pre-injury fitness, residual subclinical sparing not captured by ISNCSCI — could differ systematically between arms and are sufficient on their own to generate the observed separation.
2. **No blinding of participants, therapists or assessors:** ISNCSCI motor grading is examiner-dependent and effort-dependent. Unblinded examiners aware of allocation, and participants aware of receiving an active injection, constitute a bias pathway large enough to account for differences of this magnitude. This is the most serious single limitation.
3. **No placebo:** The comparator arm received no injection procedure. The "sham" designation is a misnomer (§2.2), so the study cannot separate pharmacological effect from the effect of receiving a weekly medical intervention.
4. **Sample size of 5 per arm:** Exact tests cannot fall below $p = 0.0625$ within groups; between-group p values of 0.0079 reflect complete rank separation in a 5-vs-5 design and are compatible with modest true effects. Binary outcomes (2/5 ambulation, 2/5 AIS D) have confidence intervals so wide as to be nearly uninformative (95% CI for 2/5 ≈ 5–85%).
5. **Single centre, single investigator team, no external monitoring or independent data audit:** No adjudication committee, no source-data verification by a third party.
6. **Combination design:** Tβ4 and BPC-157 were given together, so no inference about either agent alone, or about synergy, is possible. A factorial design is required.
7. **No multiplicity control** across nine reported comparisons.
8. **Composite bladder–bowel endpoint** was a mean of percentage changes across heterogeneous domains — a statistically inelegant con-

struction that can be dominated by the domain with the smallest baseline.

Implausible magnitude in both arms

The comparator arm's mean 19-point LEMS gain and 100% AIS B conversion substantially exceed published natural-history and locomotor-training benchmarks (natural-recovery review21; ICCP spontaneous-recovery guidance20). Three explanations compete:

a) unusually favourable case selection, with the 6–8 month window, young age, exclusively traumatic thoracic aetiology and 520 supervised training hours concentrating recovery potential;
b) systematic measurement drift in unblinded serial ISNCSCI examination by the same examiners, which inflates both arms;
c) classification error at baseline, if participants recorded as AIS B in fact had subclinical motor sparing (AIS C with unrecordable grades). We cannot exclude (b) or (c). Independent blinded re-examination of a subset, and ideally neurophysiological corroboration, would be needed to distinguish them. Until then, the absolute values reported here should carry little weight; only the relative between-arm ordering is worth carrying forward as a hypothesis.

Missing measurements

No MRI (lesion length, spared tissue cross-sectional area, diffusion metrics), no motor or somatosensory evoked potentials, no electromyography, no anti-drug antibody titres, no pharmacokinetic sampling, no biomarkers of angiogenesis or neuroinflammation (VEGF, NSE, GFAP, neurofilament light), no patient-reported outcome measures of quality of life, no spasticity quantification, no pain scores, and no follow-up beyond week 26. There is therefore no objective, examiner-independent corroboration of any neurological finding — an omission that a successor trial must close, because blinded neurophysiology is what would render the motor findings credible.

Regulatory and product limitations

Neither agent is approved for this or any indication. BPC-157 appears on the FDA's list of bulk drug substances presenting significant safety risks in compounding, with explicit immunogenicity and peptide-characterisation concerns (FDA36), and FDA's review found no adequate clinical studies in relevant populations (briefing document37). Both are WADA category S0 substances, prohibited in sport at all times (WADA 2026 list38). Product provenance and long-term safety at these cumulative exposures (42.9 mg Tβ4, 20.8 mg BPC-157 over 26 weeks) remain unestablished, and theoretical concerns about pro-angiogenic peptides and occult neoplasia cannot be addressed by a 6-month study in 5 people.

Accordingly, nothing in this report should be construed as supporting clinical use of either peptide for spinal cord injury outside a properly regulated, ethically approved and adequately monitored trial.

Recommendations for a confirmatory trial

Element	Specification
Design	Randomised, double-blind, placebo-controlled; 2×2 factorial (Tβ4 ± BPC-157) to resolve individual contributions
Control	Matching subcutaneous placebo of identical volume, appearance and schedule; identical rehabilitation dose
Blinding	Participants, therapists, and two independent ISNCSCI examiners who never see allocation or prior scores
Sample size	≥ 30 per arm; powered on a 6-point LEMS between-group difference (assuming SD 6, α 0.05, power 0.80, ~20% attrition)
Stratification	Neurological level (T1–T6 / T7–T12) and post-injury interval
Primary outcome	LEMS change at 26 weeks, blinded assessment
Key secondary	WISCI-II; TCT-SCI; ISNCSCI sensory totals; SCIM-III; NBD score; urodynamics; AIS conversion
Objective corroboration	Serial MRI with diffusion metrics; motor and somatosensory evoked potentials; surface EMG of key myotomes
Biological substudies	Pharmacokinetics of both peptides; anti-drug antibody titres; VEGF, GFAP, NFL, NSE panels
Dose exploration	Dose-ranging arm, given the two-to-three-log gap between this regimen and preclinical Tβ4 exposures
Follow-up	52 weeks minimum, with a 5-year safety registry given pro-angiogenic mechanism
Governance	Multicentre; independent DSMB; central ISNCSCI adjudication; prospective registration with published SAP before unblinding

Conclusion

In this 26-week open-label controlled pilot in 10 level-matched adults with subacute AIS-B thoracic SCI, weekly subcutaneous thymosin β4 1.65 mg plus BPC-157 0.8 mg added to 520 hours of intensive rehabilitation was feasible, achieved 100% adherence and retention, and produced no serious adverse events. The peptide arm reached a mean LEMS of 29.4/50 (58.8% of maximum) versus 19.0/50 (38.0%) with rehabilitation alone — a 35.4% relative shortfall in the comparator arm — with concordant advantages in sensory scores, ZPP migration, trunk control, ambulation milestones and bladder–bowel function. The mechanistic coherence of the pattern, its progressive rather than front-loaded divergence, and its anatomical gradient are encouraging.

These findings are nevertheless not evidence of efficacy. The absence of randomization, blinding and placebo, a sample of five per arm, recovery magnitudes in both arms exceeding published benchmarks, administered doses far below preclinical exposures, and the complete absence of examiner-independent objective corroboration together mean that non-pharmacological explanations remain fully viable. The appropriate conclusion is that this combination merits, and now justifies, a properly powered randomised double-blind placebo-controlled factorial trial with blinded neurophysiological endpoints — and nothing beyond that.

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Declarations

Ethics approval and consent to participate. Approved by the institutional ethics committee of the participating neurological research centre, approval number NUX-2025-13/23/PTP, granted 13 January 2025. Approval preceded enrolment of the first participant. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants, including documented acknowledgement of the investigational, non-approved regulatory status of both peptides and of the absence of blinding and randomisation.

Trial registration: Registro Público Cubano de Ensayos Clínicos (RPCEC), identifier RPCEC00000567, registered 2025. The RPCEC is a WHO ICTRP primary registry; the public record is searchable at https://rpcec.sld.cu. Journals applying ICMJE policy require prospective registration before enrolment of the first participant.

Consent for publication: Obtained from all participants for publication of de-identified individual-level data.

Availability of data: Individual participant data for all 10 participants are reported in full in Tables 3–8; the locked analysis dataset and analysis scripts are available from the corresponding author on rea-

sonable request.

Competing interests: Nothing to disclose.

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Author contributions (Credit taxonomy): Pritam Majumdar — conceptualization, methodology, investigation, formal analysis, data curation, visualisation, writing (original draft). Surbhi Kaura — methodology, investigation, validation, data curation, writing (review and editing). Ulduz Jafarova — investigation, project administration, resources, supervision, writing (review and editing). Georgios Matis- Review of the Manuscript and Editing, Monzurul Alam- Review and Editing the manuscript, Antony Rodriguez- Data analysis, Visualization and Editing and review the manuscript.

Reporting guideline: Reported with reference to the CONSORT extension for pilot and feasibility trials; the non-randomised allocation means TREND/STROBE elements also apply, and readers should note that this study does not meet CONSORT criteria for a randomised trial.

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