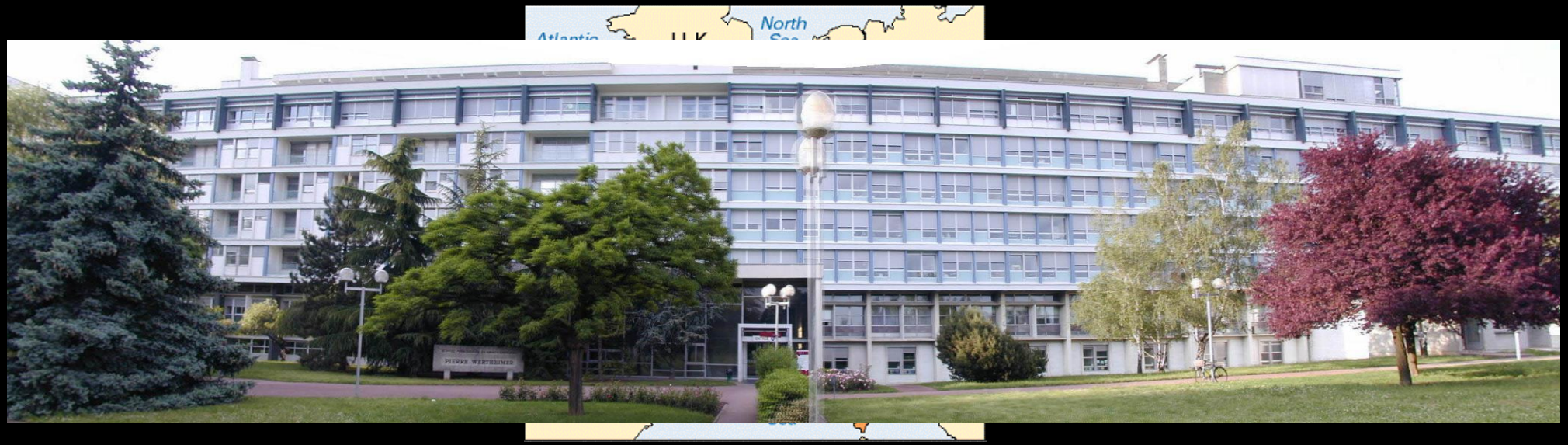
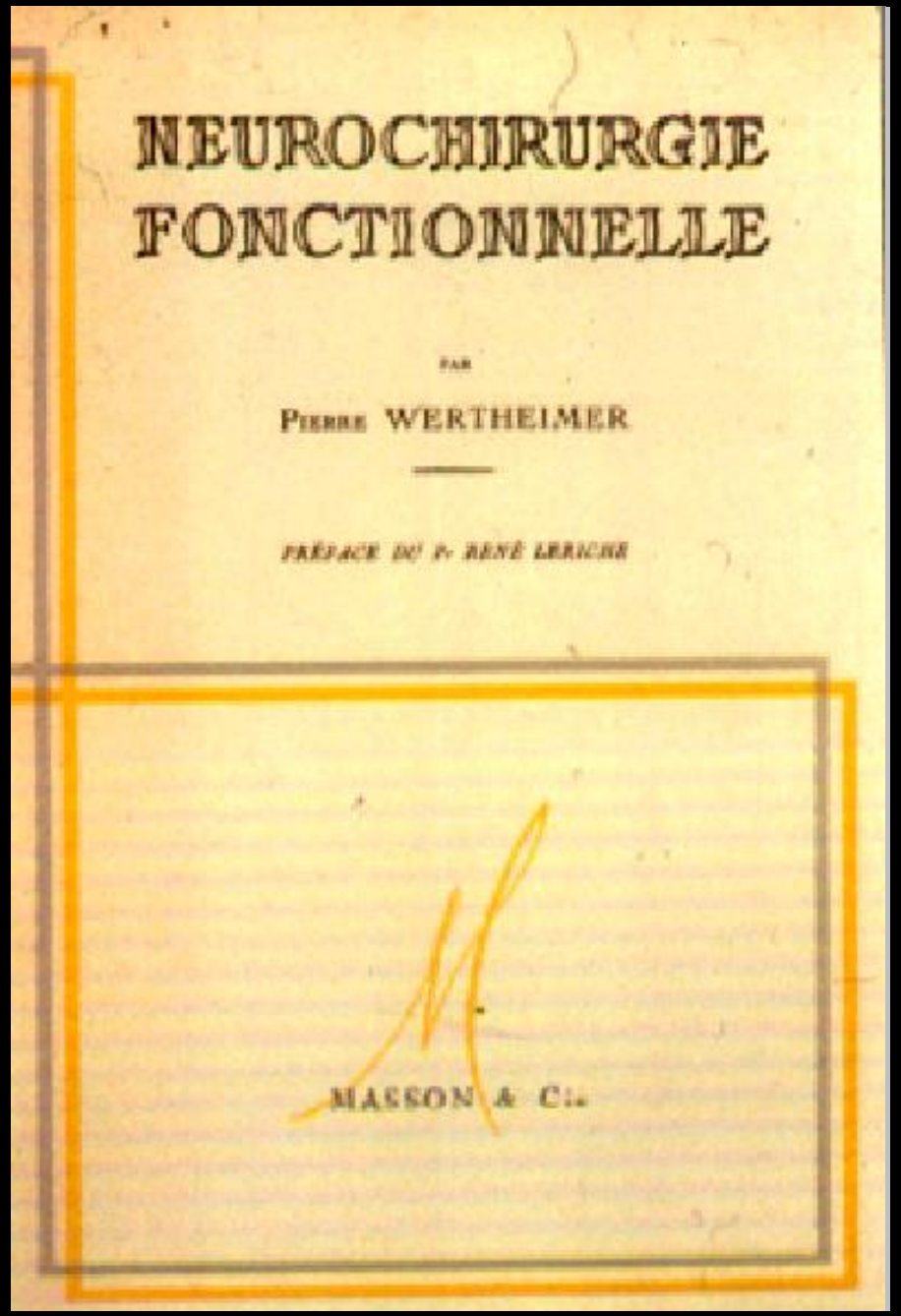
Ziconotide for spinal cord injury related pain

Andrei BRINZEU
Lyon, France



Hopital Neurologique de Lyon “Pierre Wertheimer”


Pierre Wertheimer



NEUROCHIRURGIE FONCTIONNELLE

PAR

PIERRE WERTHEIMER

Professeur à la Faculté de Médecine de Lyon

Préface du Professeur René LERICHE

Definition

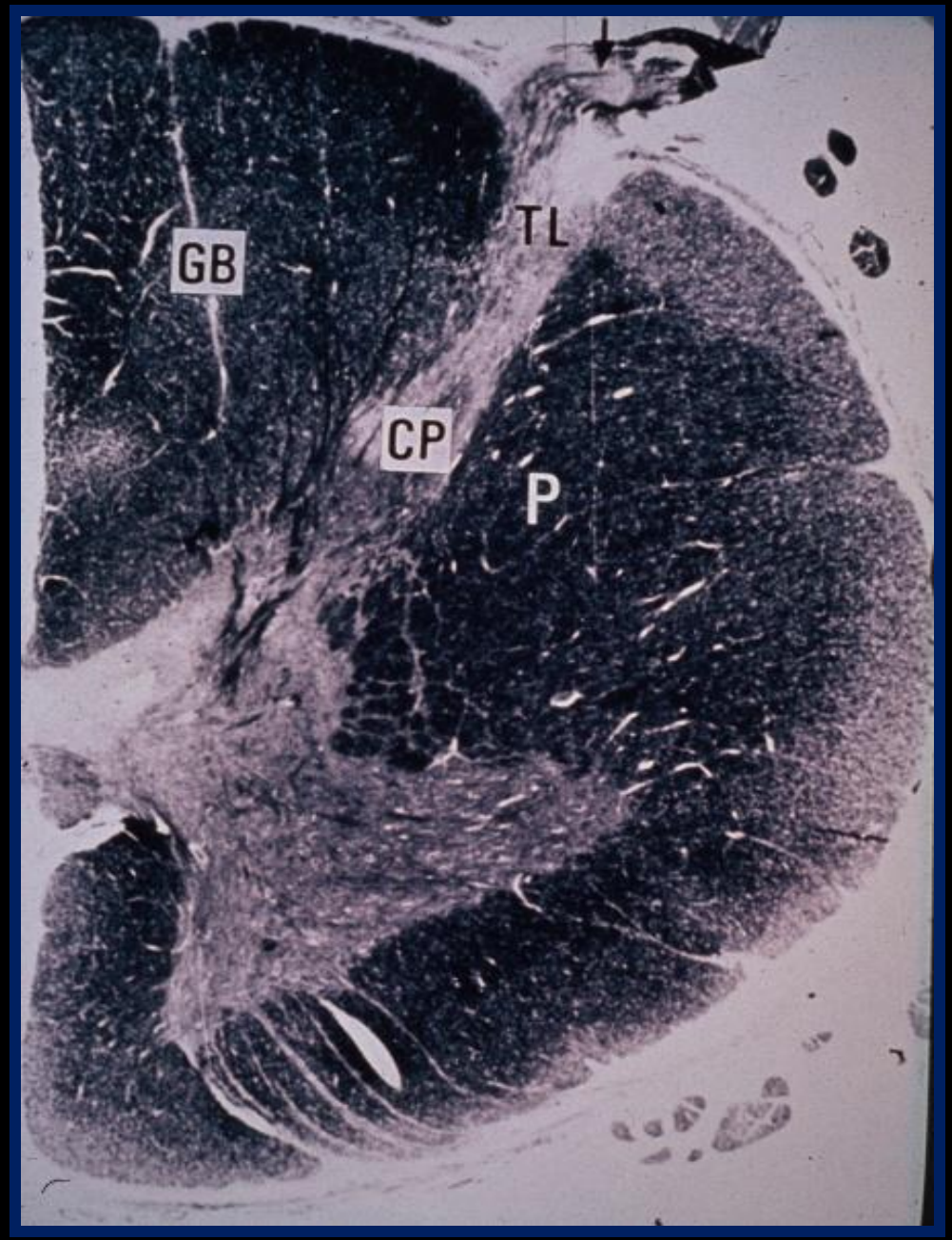
The procedures may be either **ablation of iritative foci**
or **interuption of excitatory pathways**

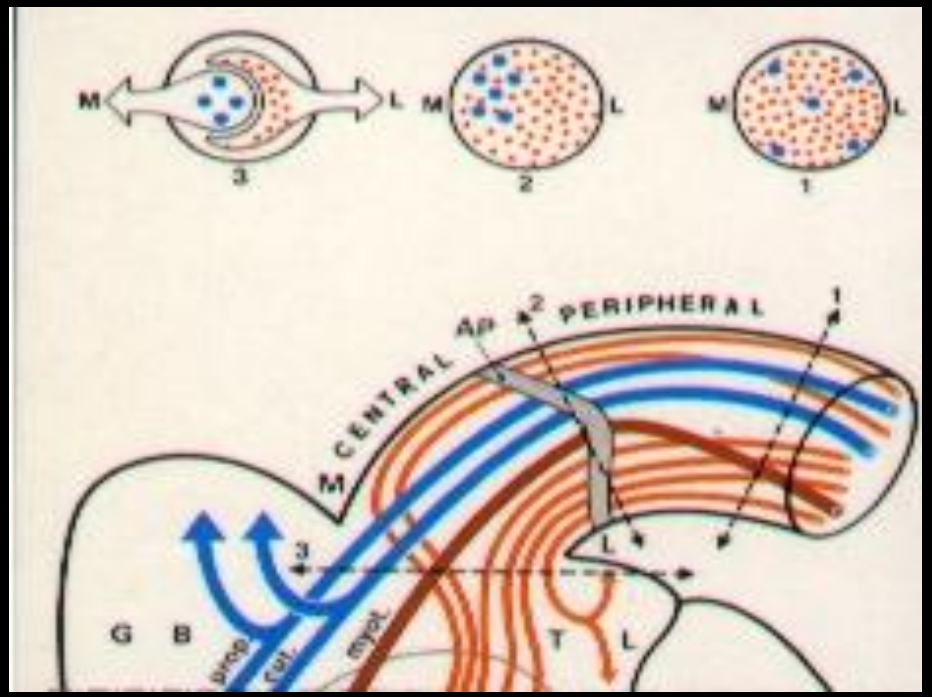
In the future new methods will be devised to compensate for the **dysfunction of inhibitory control systems**

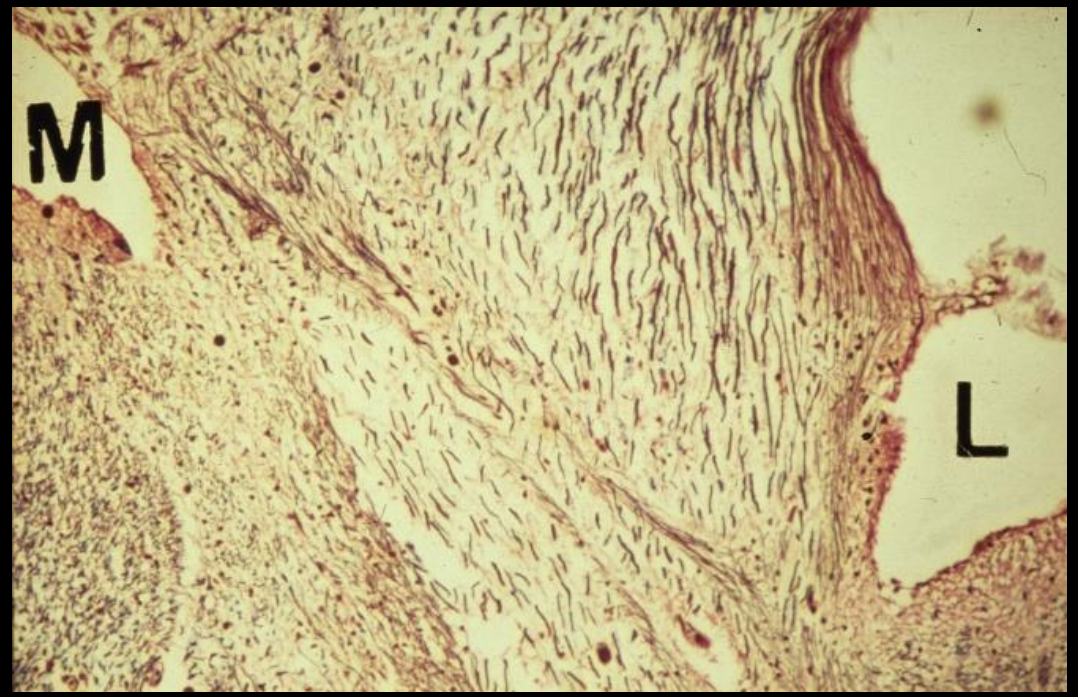
Pierre WERTHEIMER
in « Neurochirurgie Fonctionnelle » , 1956

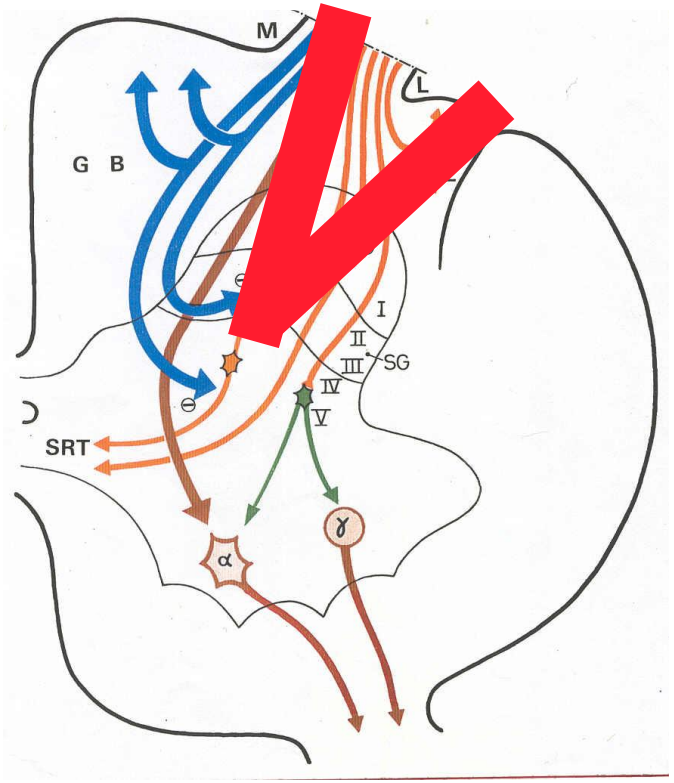
Surgery for Pain

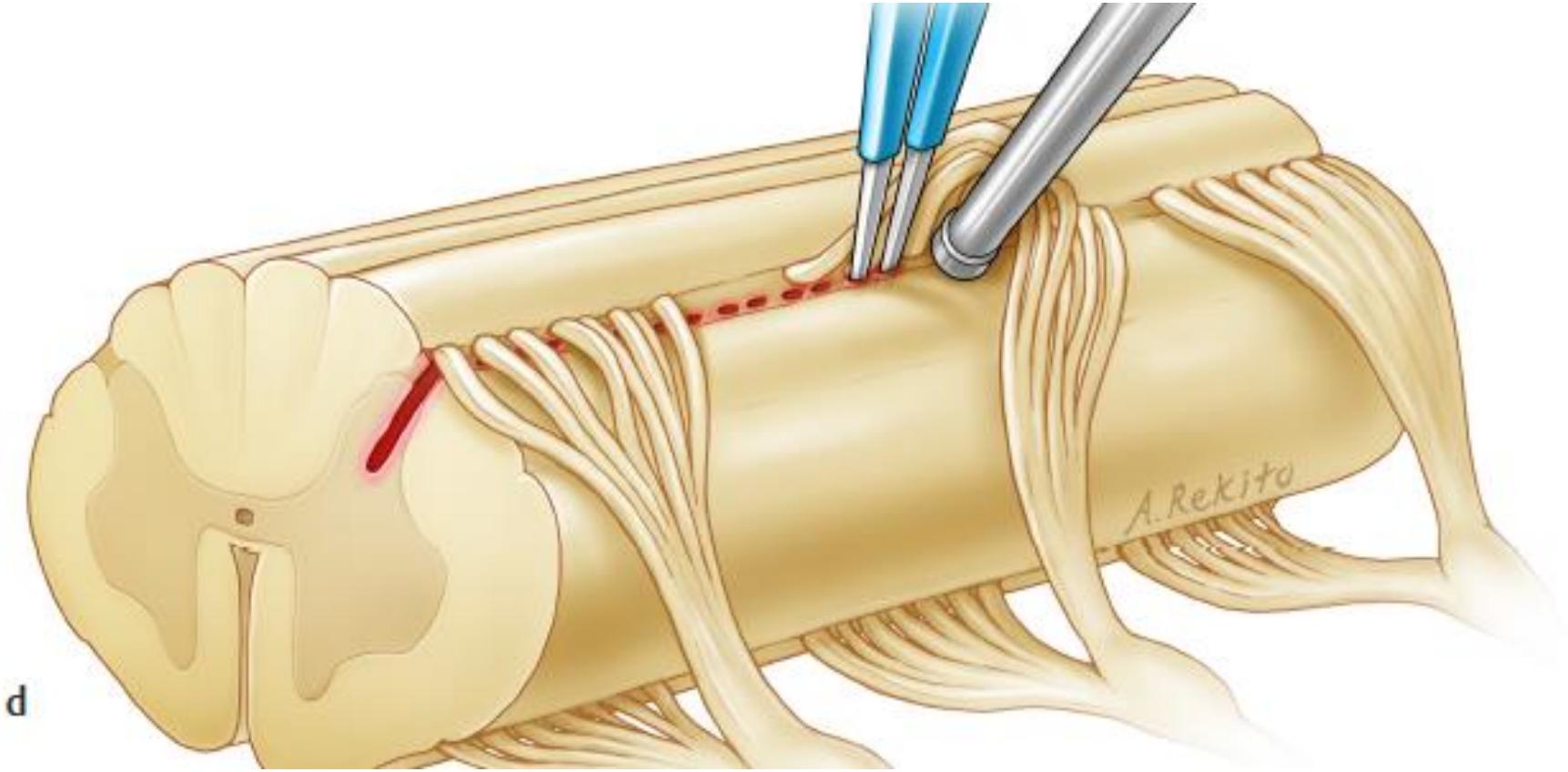

Textbook of
PAIN
APUZZO
HUMAN
CEREBRAL REVASC
SONY
30
20


GB
TL
CP
P


M
L
3
2
1
CENTRAL
PERIPHERAL
G
B
T
L


M
L





d

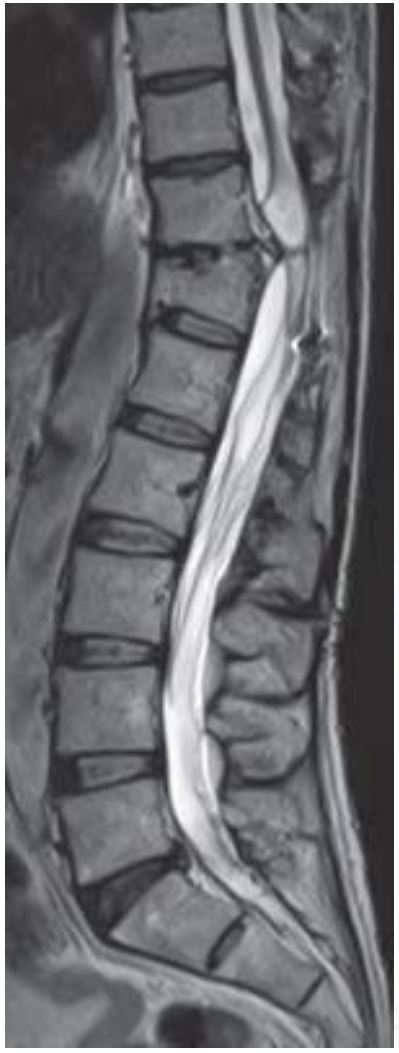
Intrathecal **ziconotide** for severe **refractory neuropathic pain** due to **spinal cord lesions**.

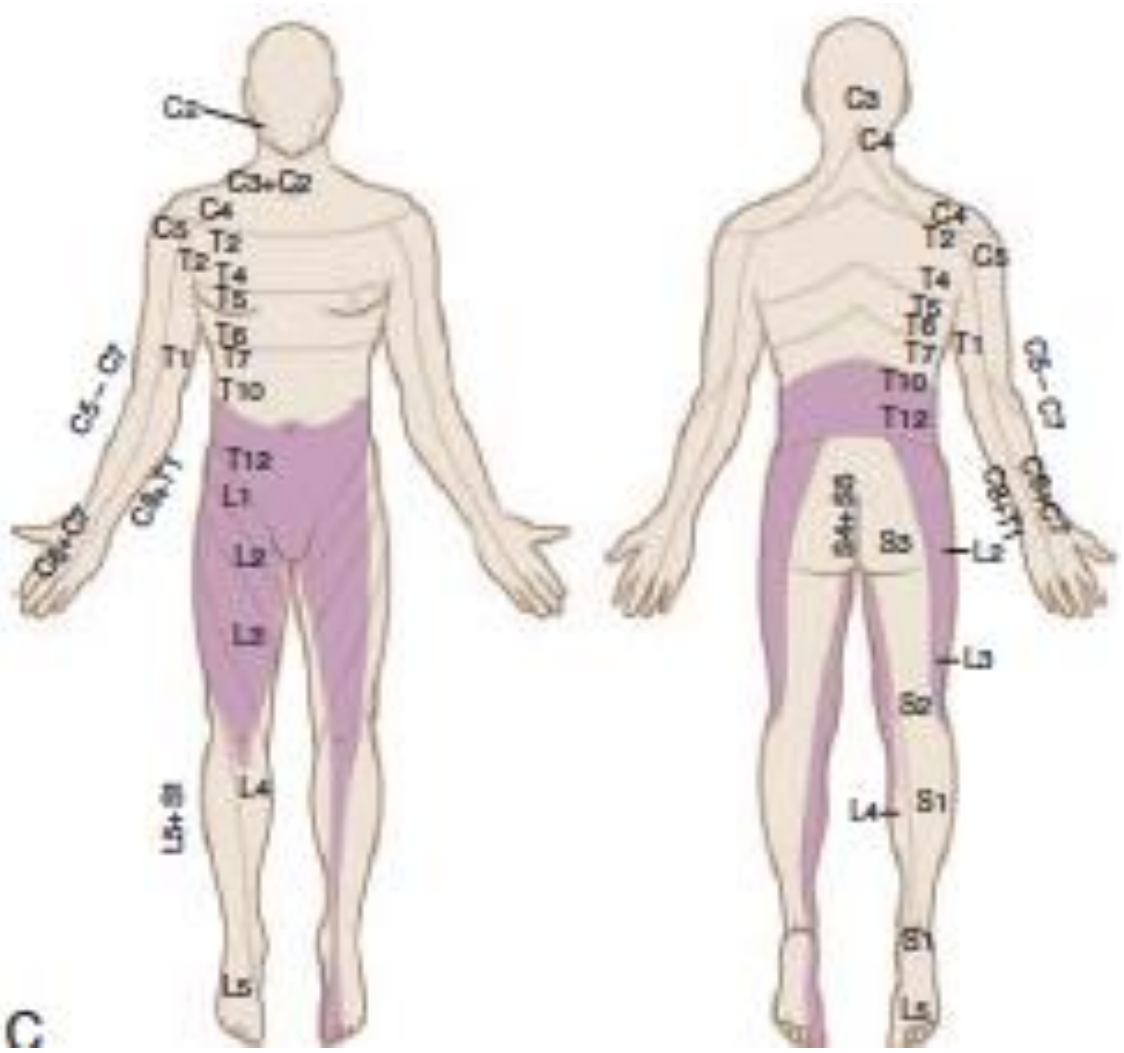
- A pilot study -

A Brinzeu, H Staquet, P Mertens

ESSFN Madrid 2016

Pain related to spinal cord lesion





Cochrane Library

Cochrane Database of Systematic Reviews

Non-pharmacological interventions for chronic pain in people with spinal cord injury (Review)

Boldt I, Eriks-Hoogland I, Brinkhof MWG, de Bie R, Joggi D, von Elm E

Authors' conclusions

Evidence is insufficient to suggest that non-pharmacological treatments are effective in reducing chronic pain in people living with SCI. The benefits and harms of commonly used non-pharmacological pain treatments should be investigated in randomised controlled trials with adequate sample size and study methodology.

PAIN

Pain 92 (2001) 159–171

www.elsevier.nl/locate/pain

Microsurgical DREZotomy for pain due to spinal cord and/or cauda equina injuries: long-term results in a series of 44 patients

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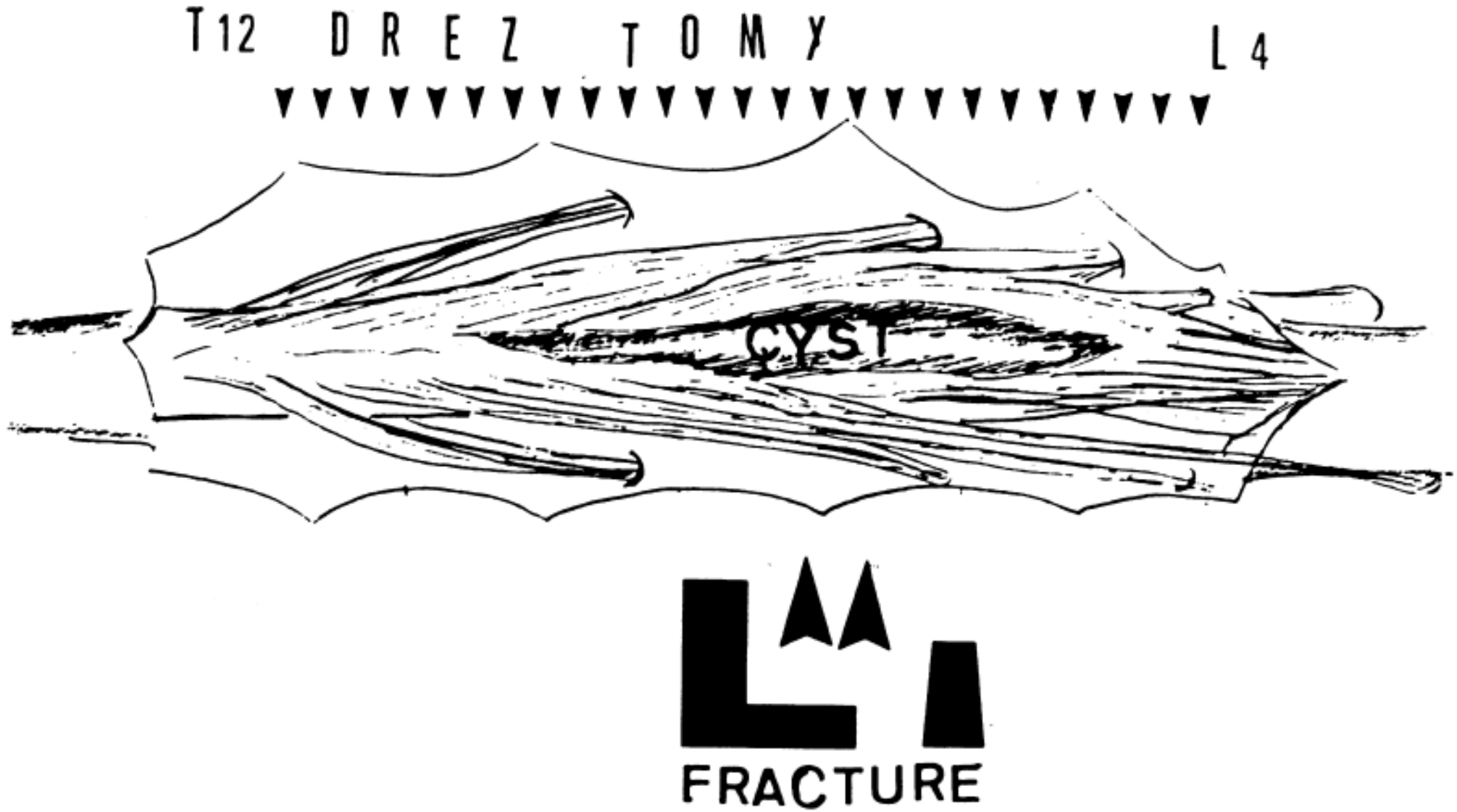
Received 1 August 2000; received in revised form 7 December 2000; accepted 12 December 2000


T12 DREZ TOMY L4
CYST
L4
FRACTURE

Abstract

Acoording to the literature estimations, 10–25% of patients with spinal cord and cauda equina injuries eventually develop refractory pain. Due to the fact that most classical neurosurgical methods are considered of little or no efficacy in controlling this type of pain, the authors had recourse to microsurgery in the dorsal root entry zone (DREZ). This article reports on the long-term results of the microsurgical approach to the dorsal root entry zone (DREZotomy) in a series of 44 patients suffering from unbearable neuropathic pain secondary to spine injury. The follow-up ranged from 1 to 20 years (6 years on average). The series includes 25 cases with conus medullaris, 12 with thoracic cord, four with cauda equina and three with cervical cord injuries. Surgery was performed in 37 cases at the pathological spinal cord levels that corresponded to the territory of the so-called 'segmental pain', and in seven cases, on the spinal cord levels below the lesion for 'infralesional pain' syndromes. The post-operative analgesic effect was considered to be 'good' when a patient's estimation of pain relief exceeded 75%, 'fair' if pain was reduced by 25–75%, and 'poor' when the residual pain was more than 75% of preoperative estimations. Immediate pain relief was obtained in 70% of patients and was long-lasting in 60% of the total series. The results varied essentially according to the distribution of pain. Good long-term results were obtained in 68% of the patients who had a segmental pain distribution, compared with 0% in patients with predominant infralesional pain. Regarding pain characteristics, a good result was obtained in 88% of the cases with predominantly paroxysmal pain, compared with 26% with continuous pain. There were no perioperative mortalities. Morbidity included cerebrospinal fluid leak (three patients), wound infection (two patients), subcutaneous hematoma (one patient) and bacteremia (in one patient). The above data justify the inclusion of DREZ-lesioning surgery in the neurosurgical armamentarium for treating 'segmental' pain due to spinal cord injuries.

Keywords: Neuropathic pain; Dorsal root entry zone surgery; Spinal cord injury; Cauda equina injury

Cochrane Library

Cochrane Database of Systematic Reviews

Long-term opioid management for chronic noncancer pain (Review)

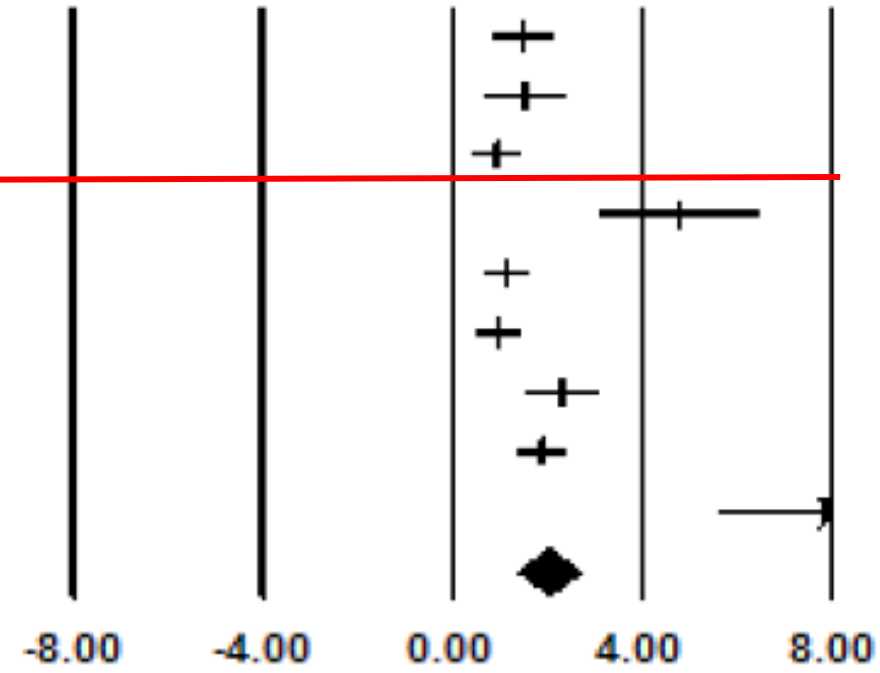
Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, Schoelles KM, Chou R

Authors' conclusions

Many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (like nausea and headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.

Figure 11. Change in Pain Score from Baseline, Intrathecal Opioids, Follow-up 6 months to 29 months (mean) (I2=87.1%)

Study Name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value	Total
Hassenbusch 1995	1.475	0.341	0.808	2.143	0.000	18
Angel 1998	1.524	0.443	0.655	2.393	0.001	11
Anderson 1999	0.926	0.267	0.402	1.449	0.001	20
Kumar 2001	4.781	0.881	3.054	6.509	0.000	16
Rainov 2001	1.128	0.251	0.637	1.620	0.000	26
Mironer 2001	0.977	0.248	0.490	1.463	0.000	24
Anderson 2003	2.306	0.390	1.541	3.072	0.000	24
Thimineur 2004	1.891	0.271	1.360	2.421	0.000	38
Shaladi 2007	7.852	1.152	5.595	10.109	0.000	24
	2.019	0.332	1.369	2.669	0.000	

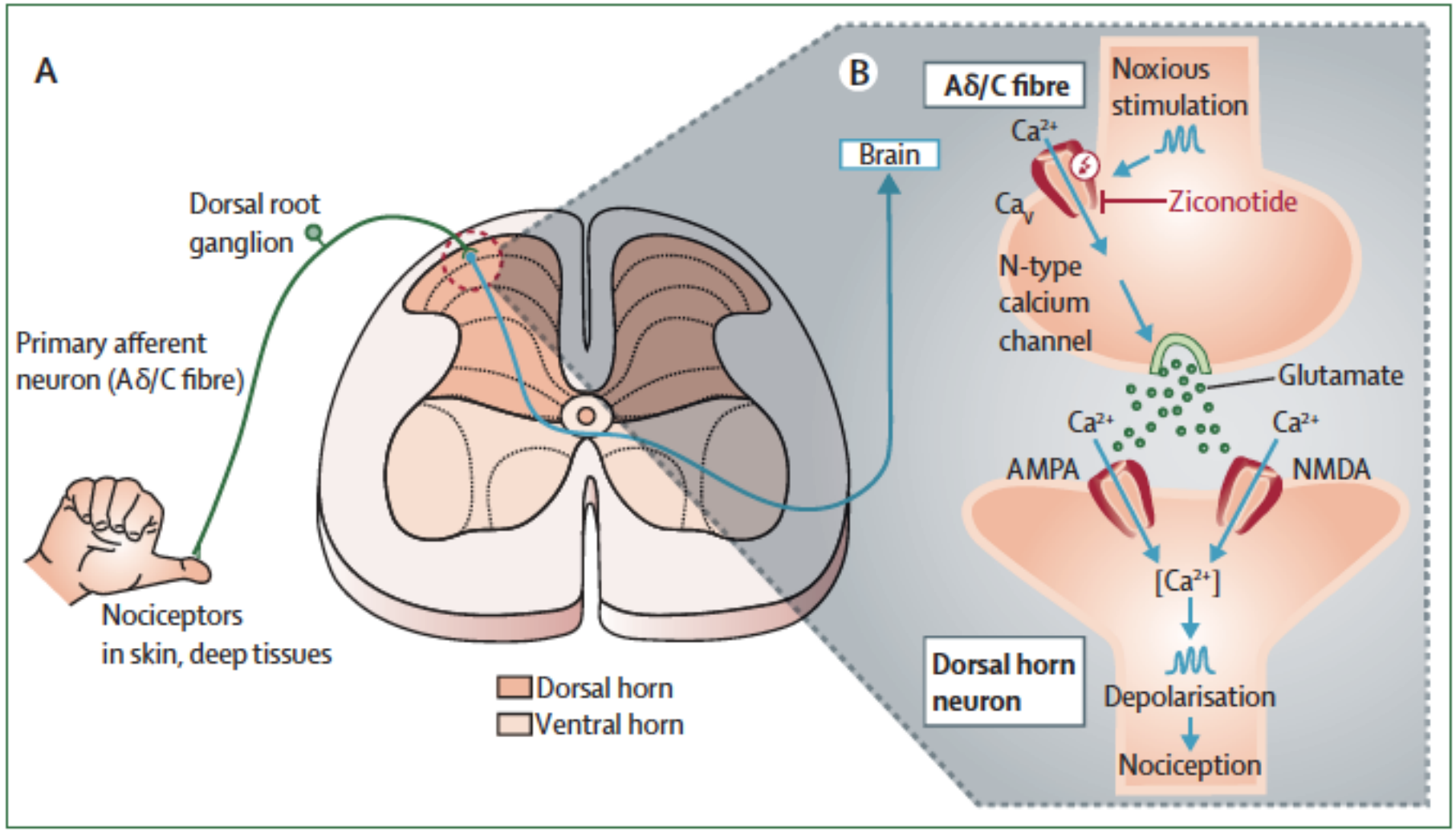


U.S Food and Drug Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CONUS MAGUS

Can immobilise prey by using a poison dart fired from one of its tentacles.


A
Dorsal root ganglion
Primary afferent neuron (Aδ/C fibre)
Nociceptors in skin, deep tissues
Dorsal horn
Ventral horn
B
Brain
Aδ/C fibre
Noxious stimulation
Ca2+
Cav
Ziconotide
N-type calcium channel
Glutamate
Ca2+
Ca2+
AMPA
NMDA
[Ca2+]
Dorsal horn neuron
Depolarisation
Nociception

Intrathecal Ziconotide in the Treatment of Chronic Nonmalignant Pain: A Randomized, Double-Blind,

ORIGINAL CONTRIBUTION

Mark S. Wallace, MD
Michael Byas-Smith, M
Dawn M
The Ziconot

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A Randomize

Peter S. Staats, MD
Thomas Yearwood, MD, P
Steven C. Charapata, MD
Robert W. Presley, MD
Mark S. Wallace, MD

Vol. 31 No. 5 May 2006 Journal of Pain and Symptom Management 393

Original Article

A Randomized, Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain

Richard L. Rauck, MD, Mark S. Wallace, MD, Michael S. Leong, MD, Michael MineHart, MD, Lynn R. Webster, MD, Steven G. Charapata, MD, Jacob E. Abraham, MD, Daniel E. Buffington, PharmD, MBA, David Ellis, MD, PhD, Ronald Kartzinel, MD, PhD, and the Ziconotide 301 Study Group

HAS

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

AVIS

14 mai 2008

PRIALT® 100 µg/ml, solution pour perfusion
Boîte de 1 flacon en verre de 1 ml – Code CIP : 569727-6
Boîte de 1 flacon en verre de 2 ml – Code CIP : 569728-2
Boîte de 1 flacon en verre de 5 ml – Code CIP : 569729-9

Cancer or AIDS Pain Non-Cancer Chronic pain

	Etude 95-001		**Etude 96-002**	
	Ziconotide (n=71)	Placebo (n=40)	Ziconotide (n=169)*	Placebo (n=86)
EVA moyen à l'inclusion (mm)	74.1± 1.8	77.9± 2.3	80.1± 1.1	76.9± 1.5
EVA moyen après 5 ou 6 jours de traitement	35.7± 3.5	61± 4.9	54.4± 2.6	71.9± 2.5
Evolution du score EVA entre l'inclusion et J5 ou J6 (%)	**51.4 (±4.6)**	**18.1 (± 6.8)***	**31.2 (± 3.4)**	**6 (± 3.1)****

* p=0.0003, ** p≤ 0.001

Repondeurs Repondeurs

34/71 7/40 54/169 11/79

Intrathecal **ziconotide** for severe **refractory neuropathic pain** due to **spinal cord lesions**.

- A pilot study -

A Brinzeu, H Staquet, P Mertens

MADRID SPAIN 2016 28 SEPTEMBER 01 OCTOBER
XXII CONGRESS OF THE EUROPEAN SOCIETY
FOR STEREOTACTIC AND FUNCTIONAL NEUROSURGERY
www.essfncongress.org

Objective

To determine efficacy of Ziconotide in the treatment of pain related to spinal cord lesions

Patient selection

Neuropathic pain associated to

spinal cord lesions

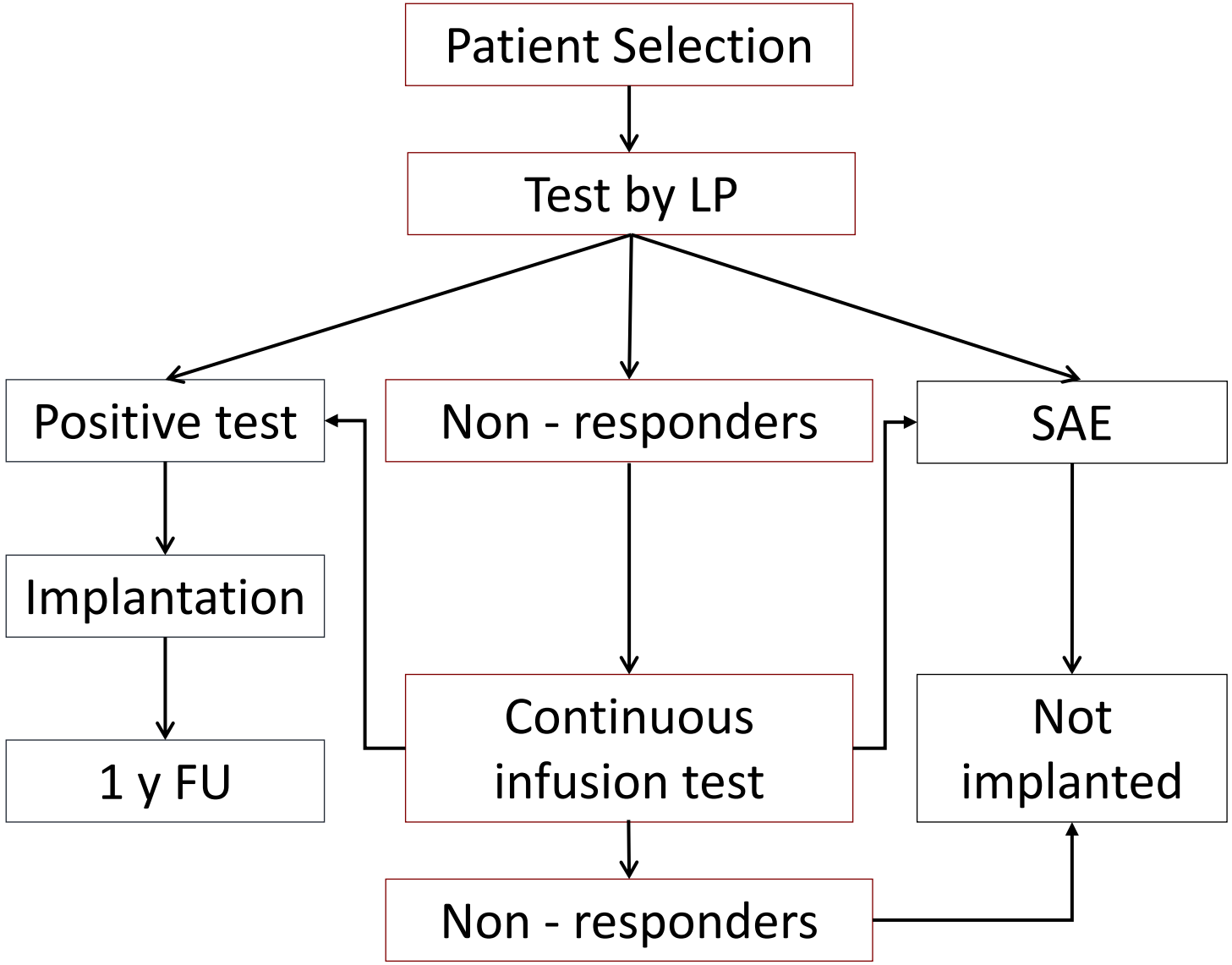
SCI – sublesional pain

Post tumor surgery

Syringomyelia

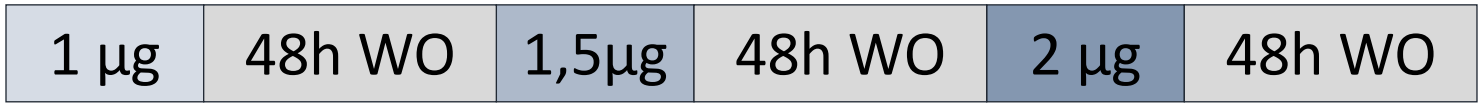
Patient group

- 20 patients
- 8 F, 12 M
- Age = 50±12 y
- Neuropathic central pain
- At-level and Below Level pain
- Various etiologies
- Refractory - therapeutic failure: NO prior surgery


Patient Selection
Test by LP
Positive test
Non - responders
SAE
Implantation
1 y FU
Continuous infusion test
Not implanted
Non - responders

LP Test

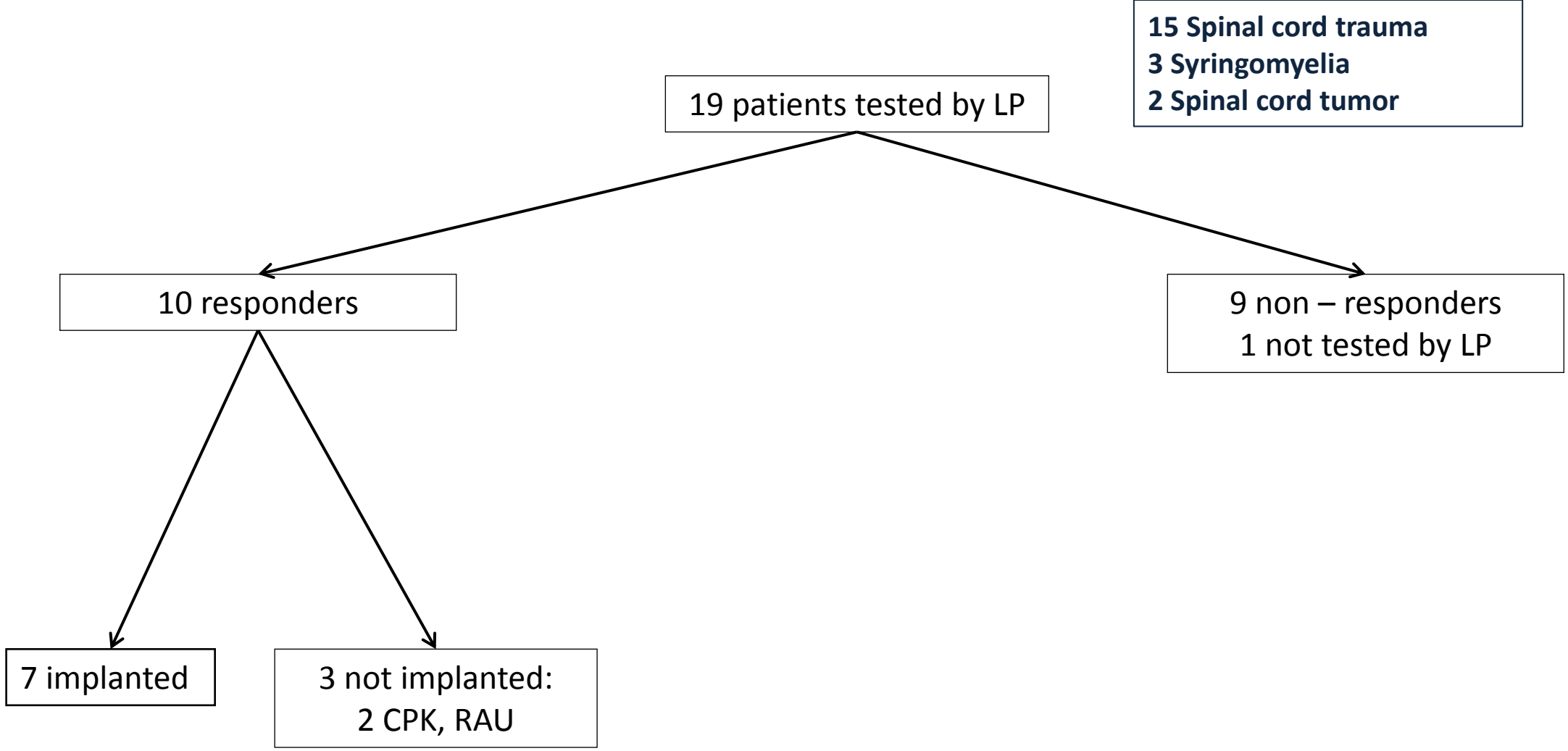
3 LP’s

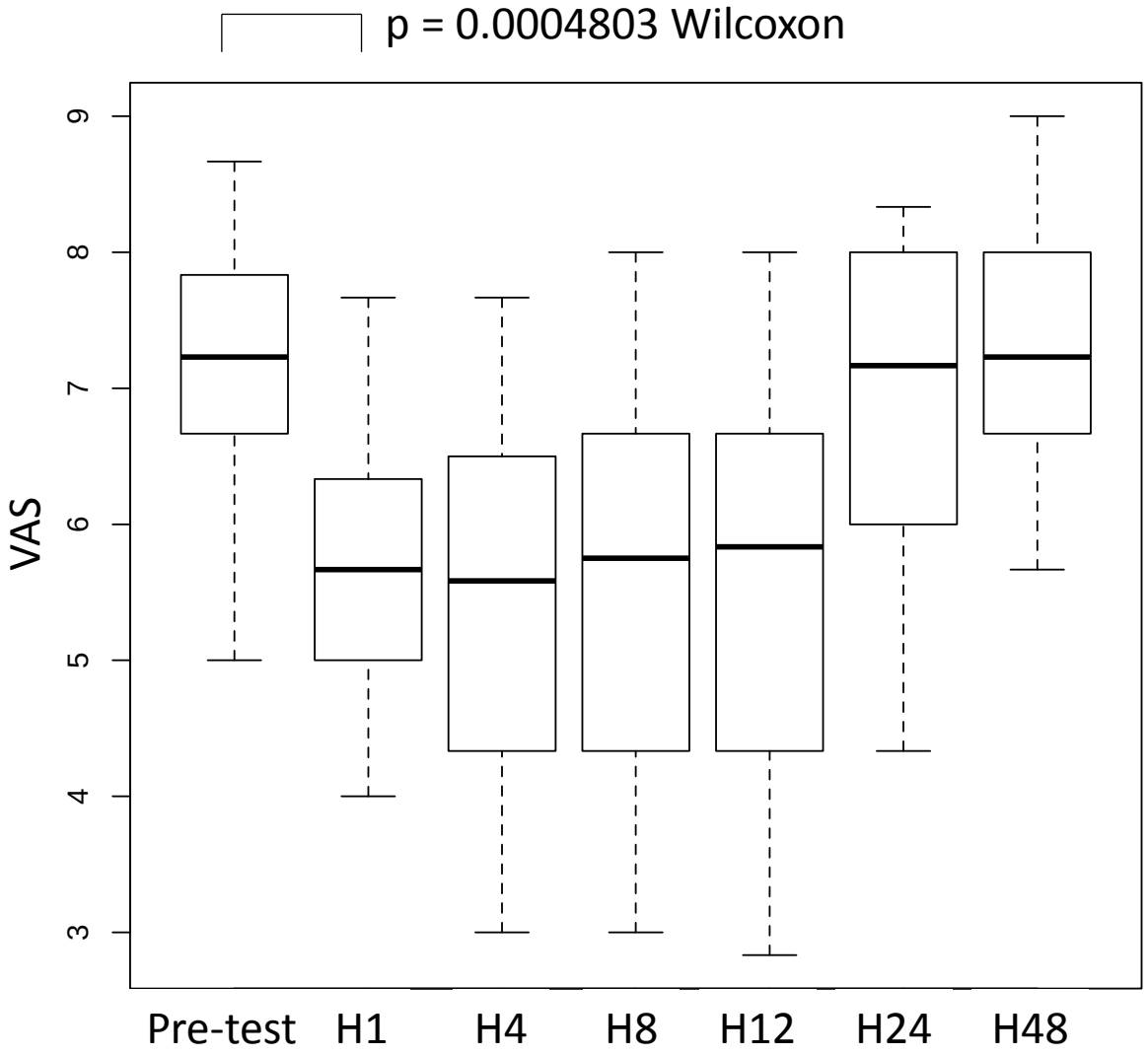


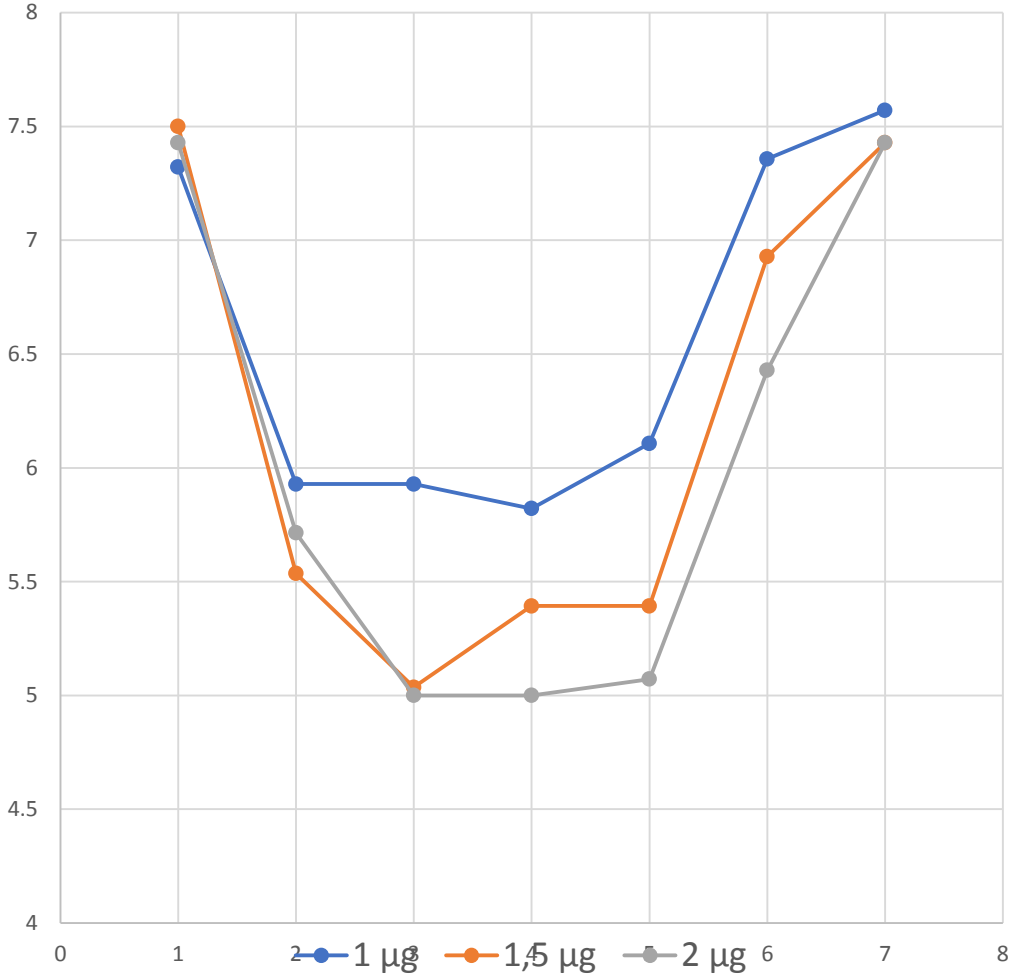
Positive test criteria

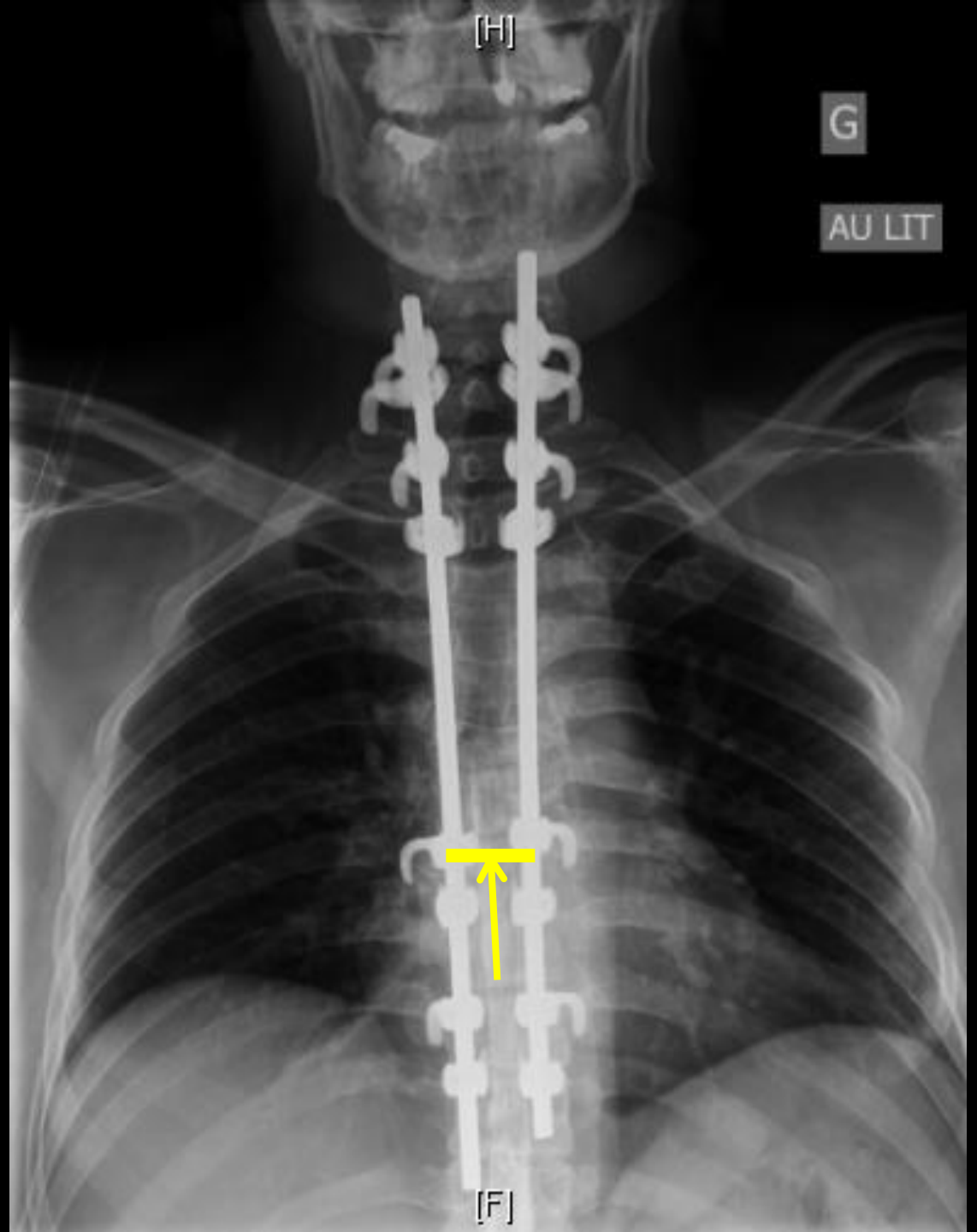
- 40% Decrease of VAS score
- 50% Reduction in paroxystic atacks
- 40% Patient satisfaction
- Absence of an SAE

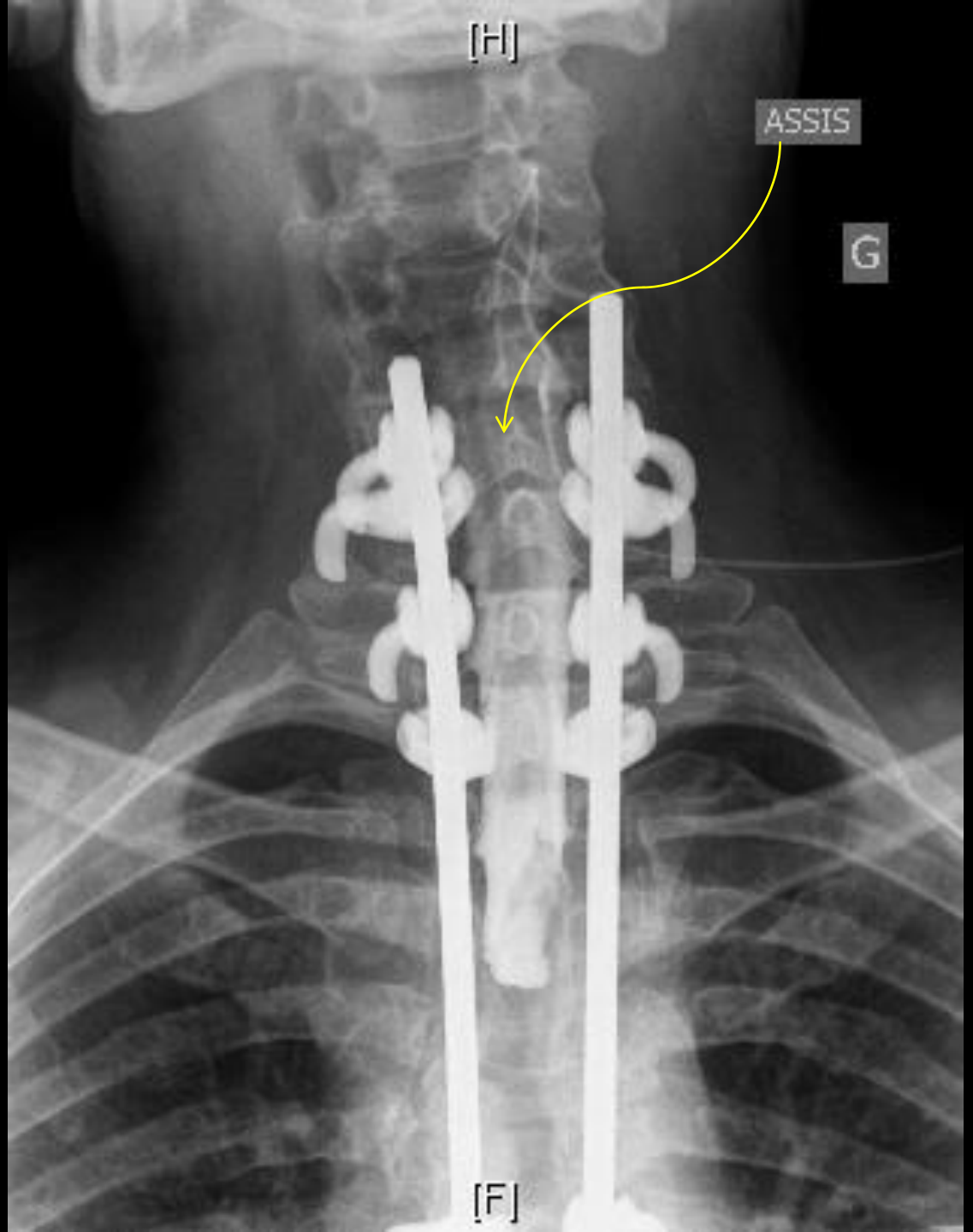
Results

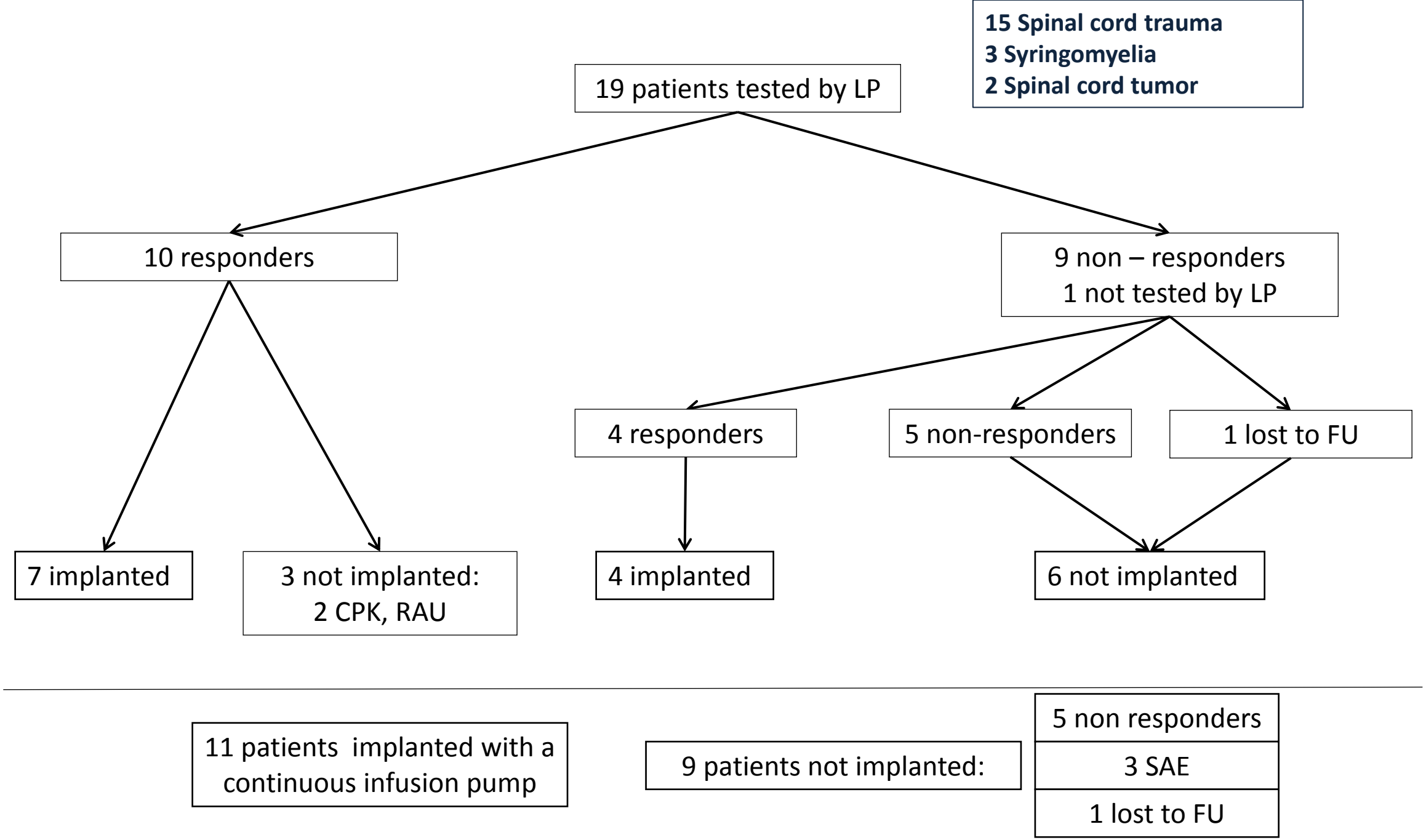

15 Spinal cord trauma
3 Syringomyelia
2 Spinal cord tumor
19 patients tested by LP
10 responders
9 non – responders
1 not tested by LP
7 implanted
3 not implanted:
2 CPK, RAU

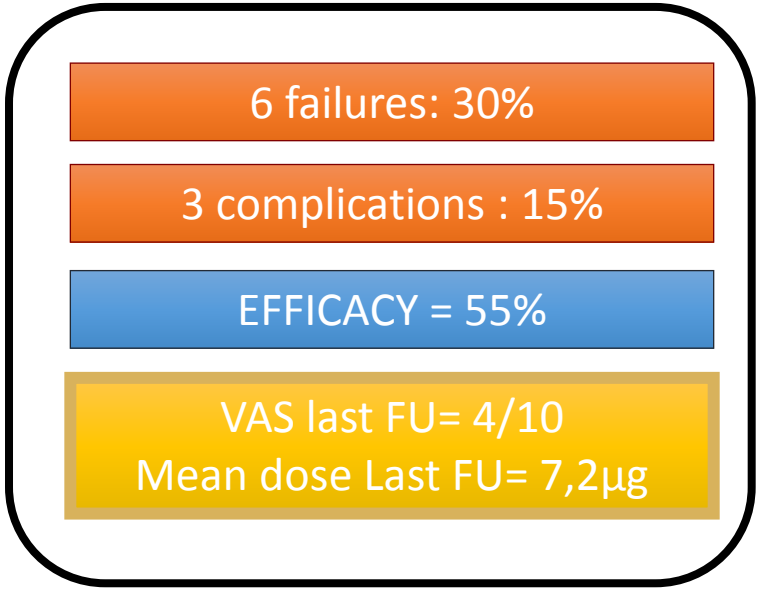

p = 0.0004803 Wilcoxon
VAS
3
4
5
6
7
8
9
Pre-test
H1
H4
H8
H12
H24
H48


8
7.5
7
6.5
6
5.5
5
4.5
4
0
1
2
3
4
5
6
7
8
1 µg
1,5 µg
2 µg

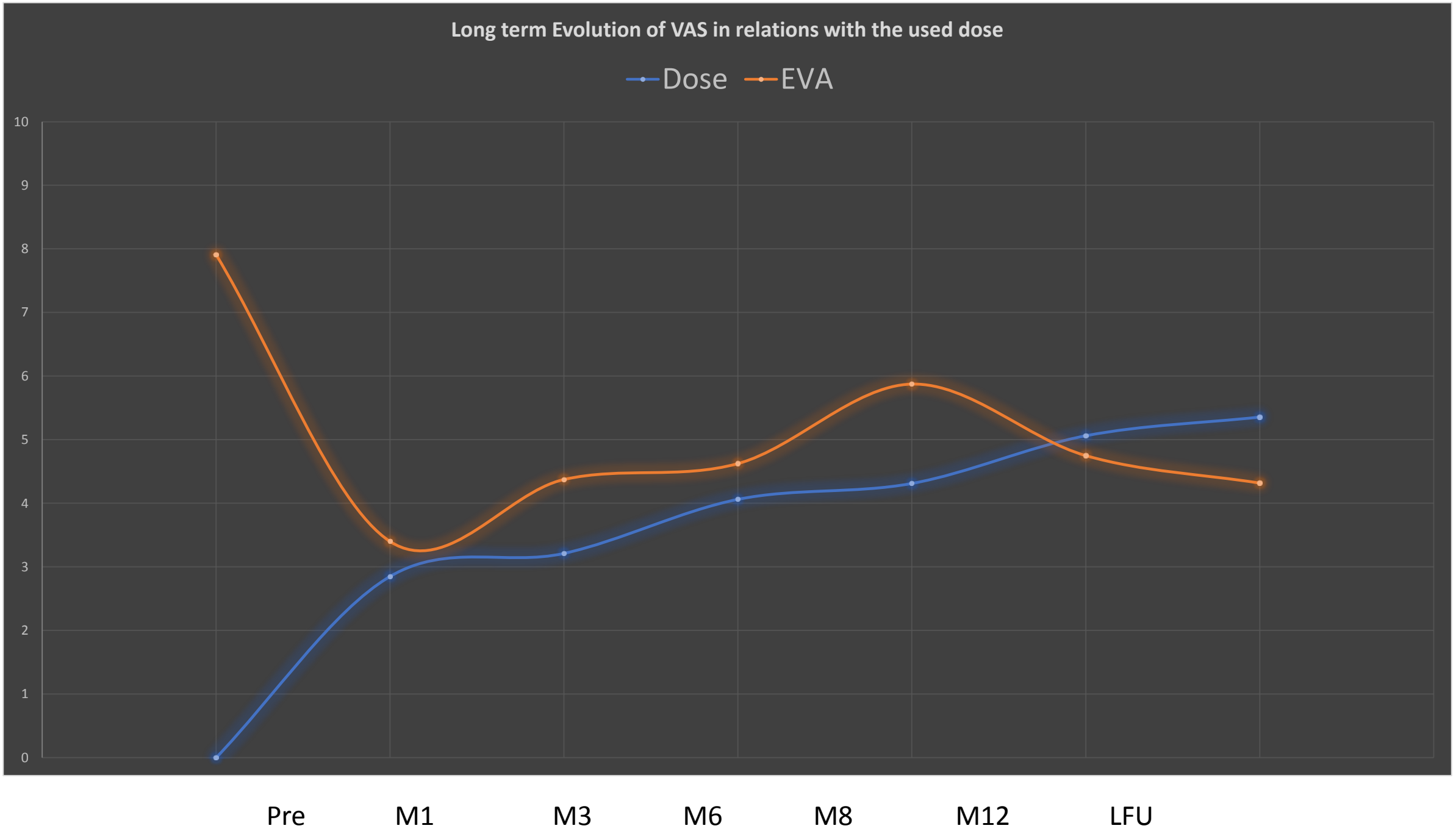

[H]
G
AU LIT
[F]

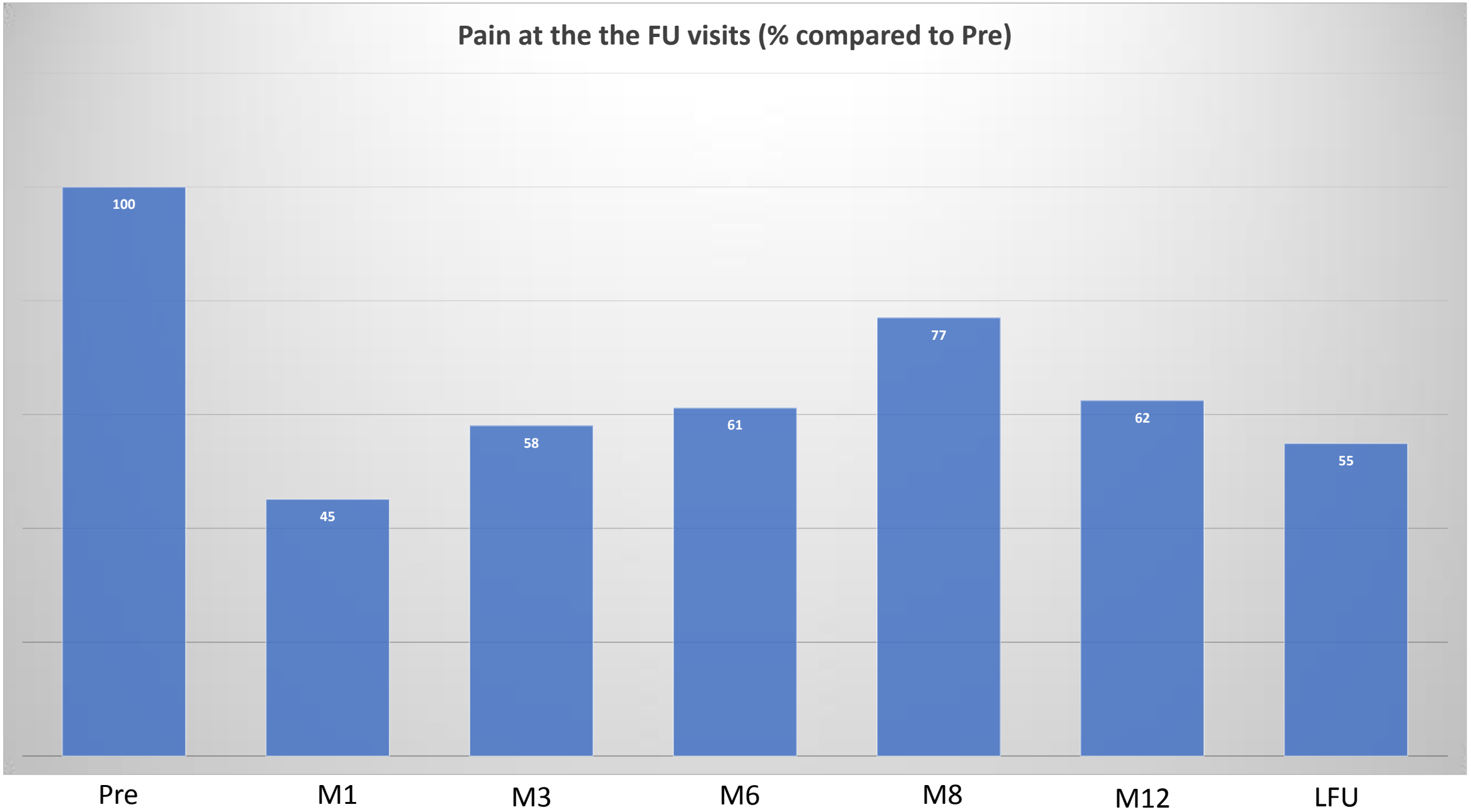

[H]
ASSIS
G
[F]


15 Spinal cord trauma
3 Syringomyelia
2 Spinal cord tumor
19 patients tested by LP
10 responders
9 non – responders
1 not tested by LP
4 responders
5 non-responders
1 lost to FU
7 implanted
3 not implanted:
2 CPK, RAU
4 implanted
6 not implanted
11 patients implanted with a continuous infusion pump
9 patients not implanted:
5 non responders
3 SAE
1 lost to FU

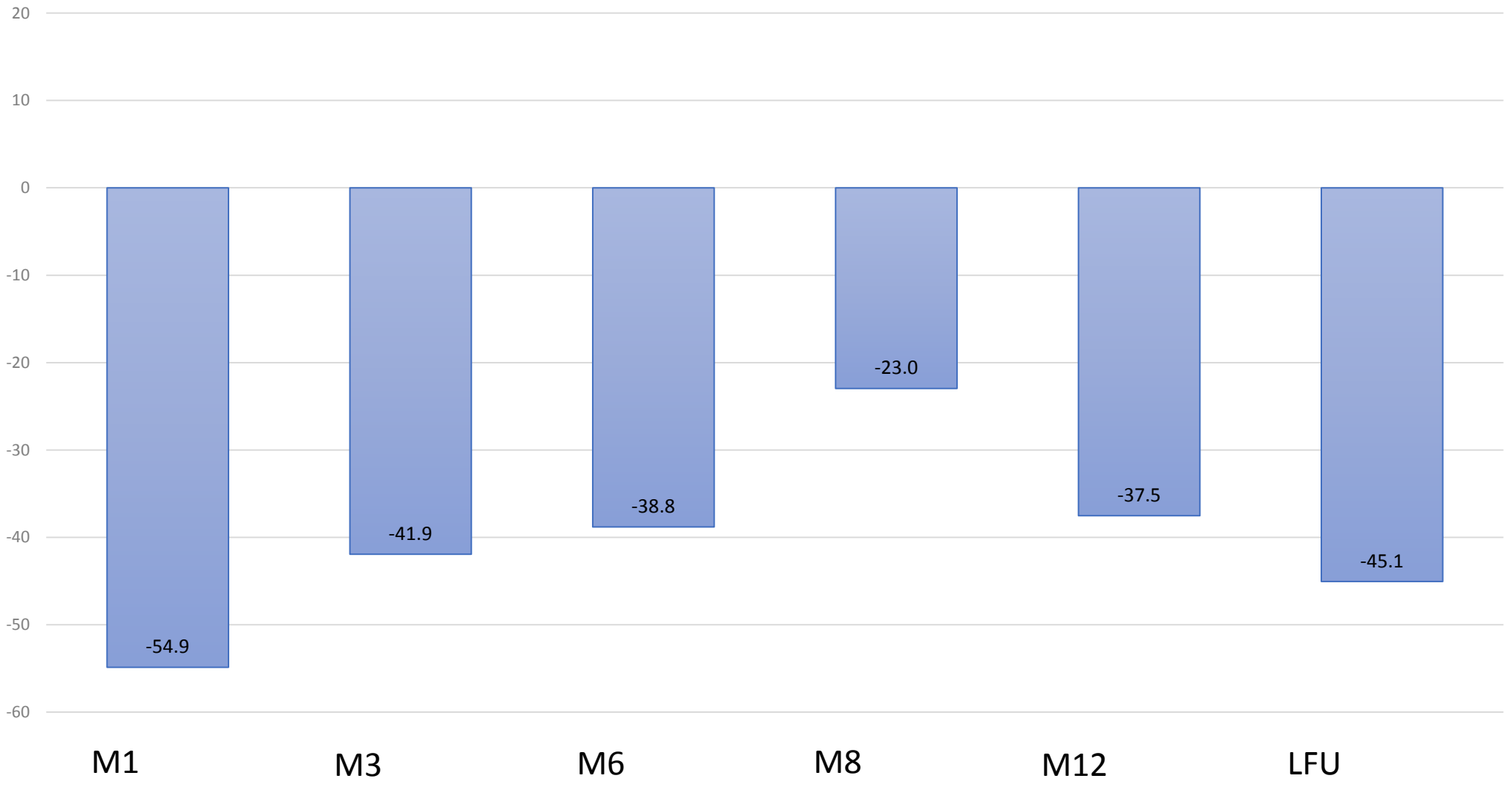

6 failures: 30%
3 complications : 15%
EFFICACY = 55%
VAS last FU= 4/10
Mean dose Last FU= 7,2µg

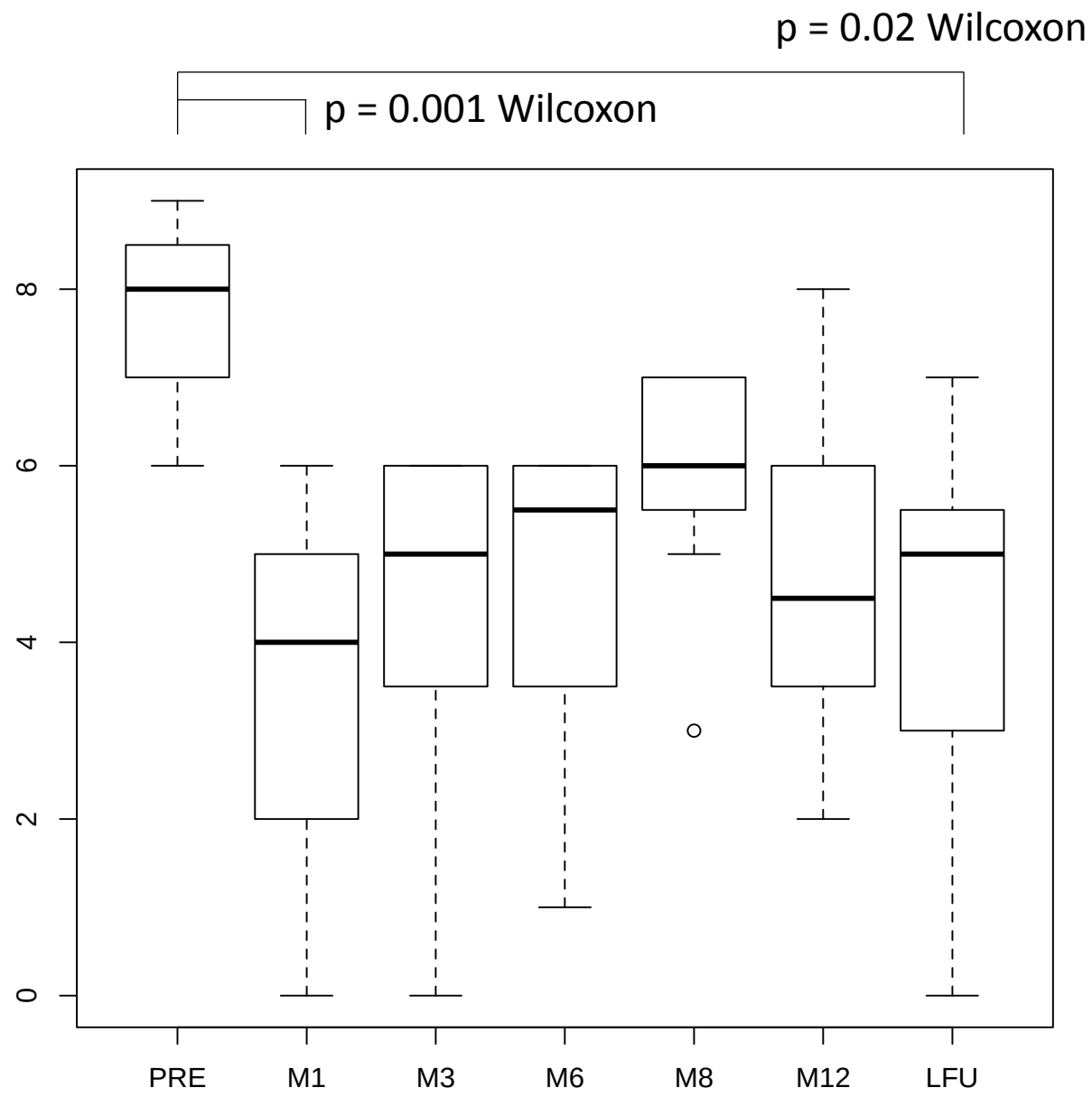
Long term results – average FU 3.8 y 11 patients

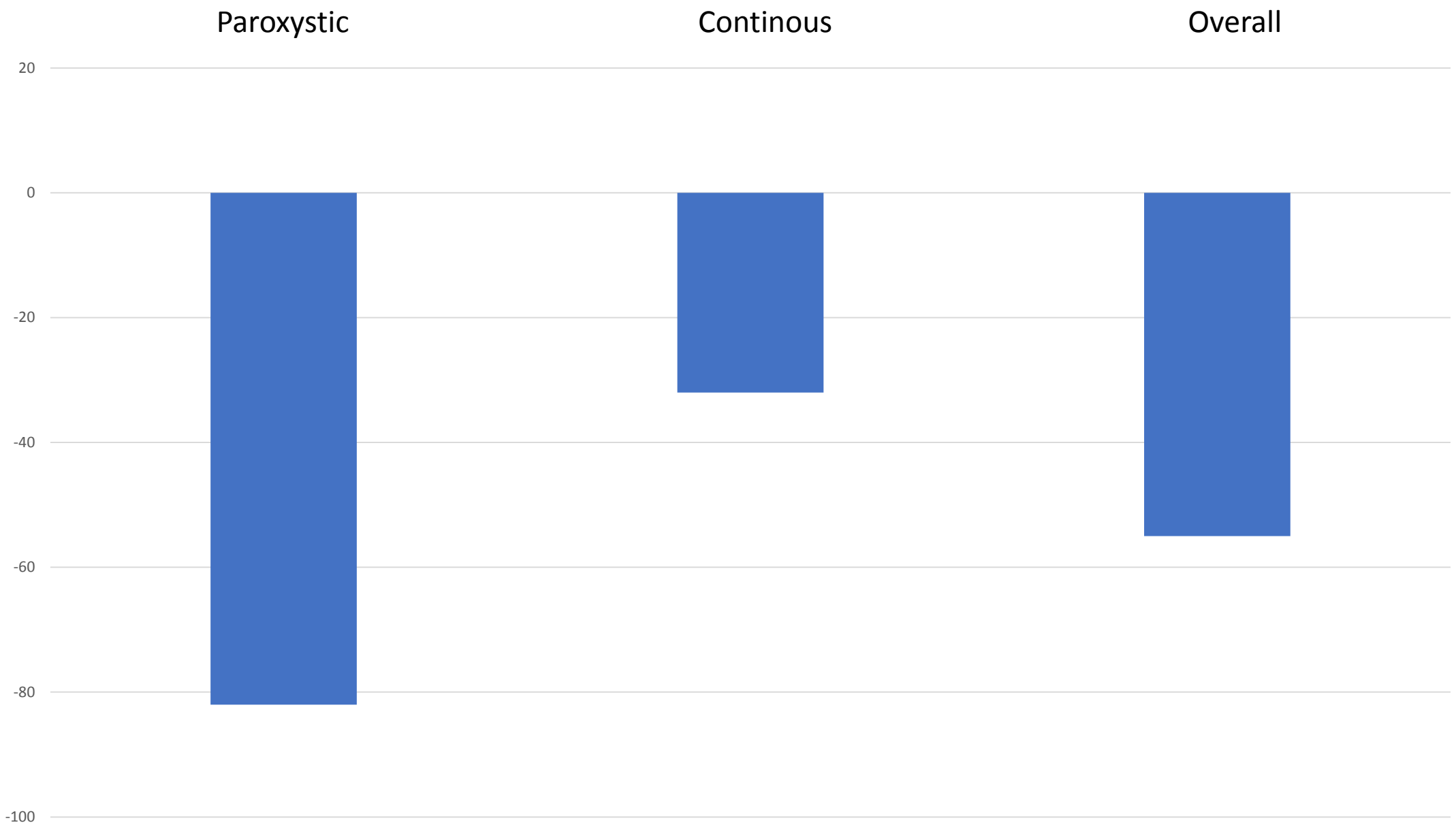

Long term Evolution of VAS in relations with the used dose
Dose
EVA
10
9
8
7
6
5
4
3
2
1
0
Pre
M1
M3
M6
M8
M12
LFU


Pain at the the FU visits (% compared to Pre)
100
45
58
61
77
62
55
Pre
M1
M3
M6
M8
M12
LFU

% decrease in VAS




p = 0.02 Wilcoxon
p = 0.001 Wilcoxon
0
2
4
6
8
PRE
M1
M3
M6
M8
M12
LFU


Paroxystic
Continous
Overall
20
0
-20
-40
-60
-80
-100

Conclusion

- Potential use of Ziconotide in SCI pain
- Half of patients are initial responders
- Significant proportion of SAE
- Dosage in question (rarely is there a long term effect at low doses)
- No RCT on this particular question

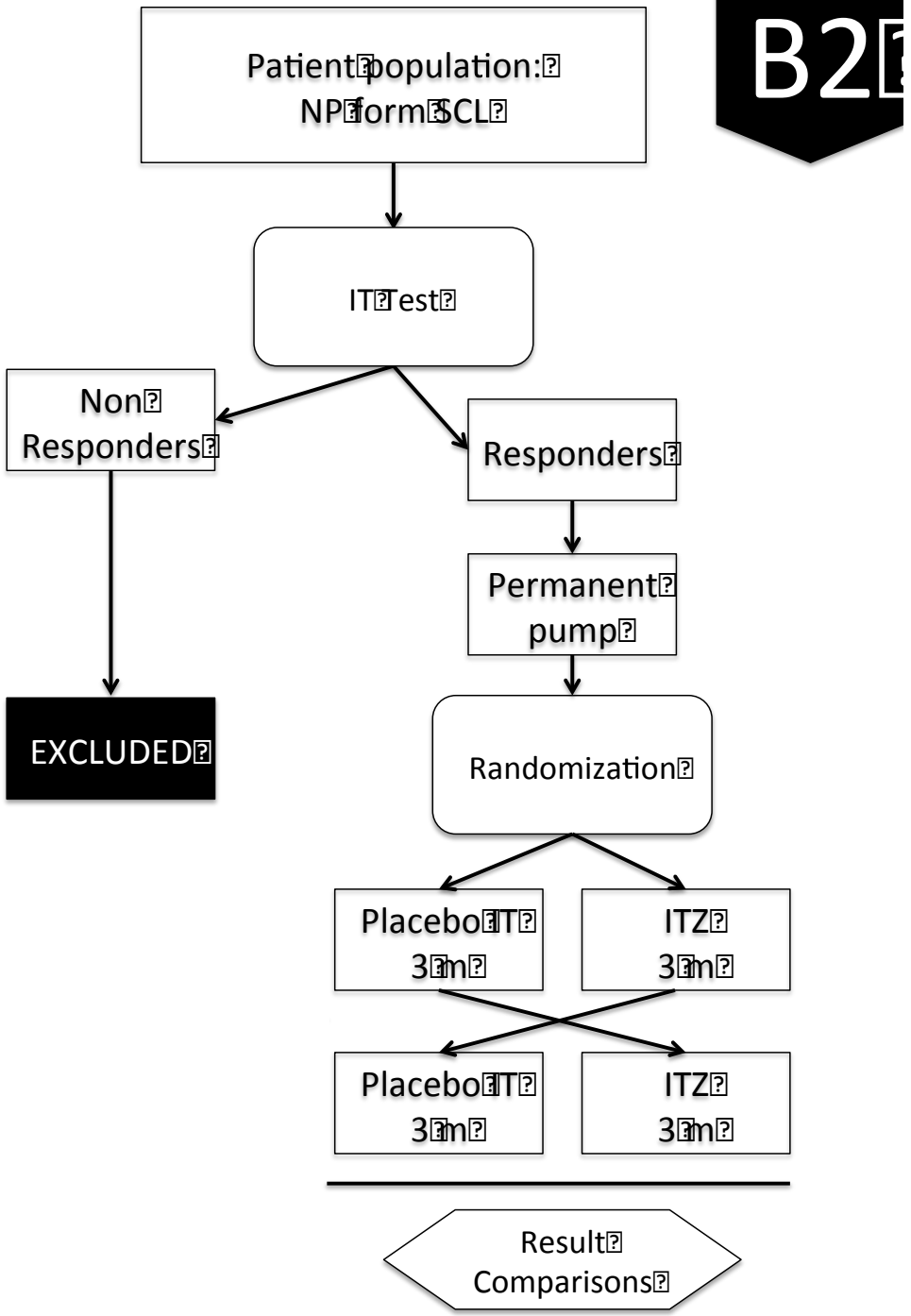
Perspective

Assessment of intrathecal Ziconotide antalgic efficacy for severe refractory neuropathic pain due to spinal cord lesions.

The *SPIDOL* Study

RCT of ITZ for SCI pain

- French multicenter study
- Physical Medicine – Recruitment
- Neurologists/algologists – follow up
- Neurosurgeons Intervention
- Funded through a national research grant (PHRC – National)


Patient population:
NP form SCL
IT Test
Non Responders
Responders
EXCLUDED
Permanent pump
Randomization
Placebo IT 3m
ITZ 3m
Placebo IT 3m
ITZ 3m
Result Comparisons

- Target 60 patients
- 1 year total follow up
- Starting recruitment 4th quarter 2018