5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 3

EAN/PNS: Novel approach in the treatment of neuropathy (Level3)

Genetic therapy in amyloid neuropathy: the future has started

Davide Pareyson
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Genetic therapy in amyloid neuropathy: the future has started

Davide Pareyson

IRCCS Foundation
C.Besta Neurological Institute
Milan - Italy

Teaching course
EAN/PNS: Novel approach in the treatment of neuropathy

5TH EAN Meeting - Oslo, 29th June 2019

1

Disclosures

- Acknowledges donations from Pfizer, LAM Therapeutics and Acceleron to support research activities of his Research Unit
- Financial support from Pfizer and Kedrion for participation in National and International Meetings
- Participation in Advisory Board of Inflectis, Alnylam and Akcea
- Consultancy for Alnylam

2

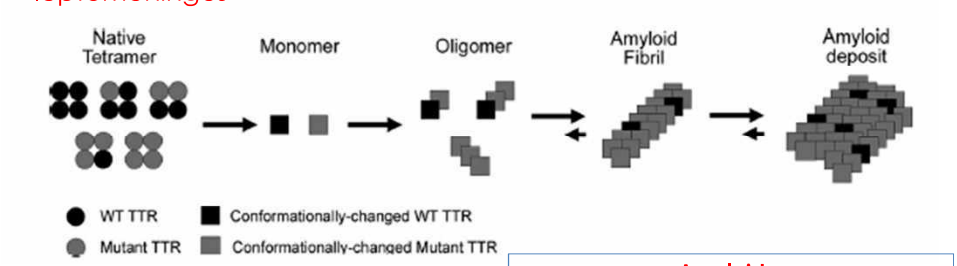
- Hereditary TTR Amyloidosis (hATTR)
- Heterogeneity of presentation and importance of early diagnosis
- Liver transplantation and TTR stabilizers
- Gene silencing (ASO and siRNA)
- New perspectives and new problems in the novel scenario

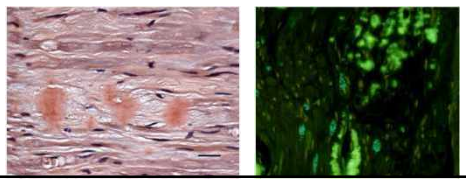
3

Hereditary Transthyretin Amyloidosis (hATTR)

Transthyretin: serum and CSF transport protein for retinol-binding protein and thyroxine; synthesized in liver (+ choroid plexus, retinal pigment epithelium)

Dominant mutations cause conformational changes and deposition as amyloid in several organs, nerve-ganglia, heart, kidney, eye, leptomeninges





Amyloid =
fibrils 7-13 nm,
core structure of beta-strands
+ other proteins glycosaminoglycans and serum amyloid P component (SAP)
Congo Red – green birefringence

4

Hereditary Transthyretin Amyloidosis (hATTR)

Autosomal dominant inheritance (>120 mutations; V30M)

Onset 10-90 yrs (**early onset / late onset**)

Lenght-dependent sensory-motor polyneuropathy

Autonomic neuropathy

Cardiomyopathy = arrhythmias, hypertrophic cm

Ocular involvement = vitreous opacities, glaucoma

Rare leptomeningeal involvement

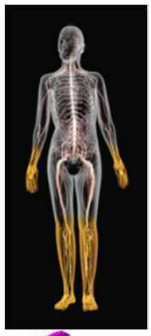
Carpal tunnel syndrome

Rapid course, **lethal if untreated** in 7-15 years

Endemic in Portugal, Sweden, Japan, Maiorca, (Brazil)

Increased recognition in **non-endemic** countries

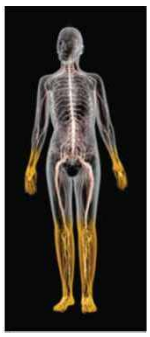
Early diagnosis of paramount importance as effective treaments available

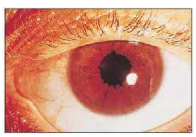


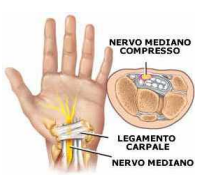
5

Typical early-onset Val30Met (Portuguese type)

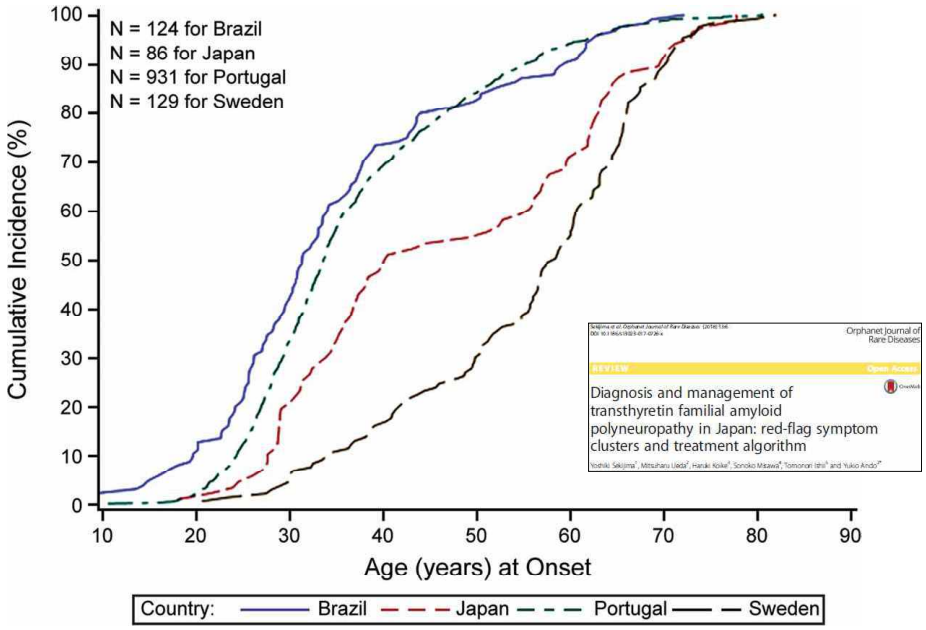
- Age of onset = peak 25-35 yrs (mean 33.5)
- Small fibre sensory neuropathy
  - Pain and thermal sensory loss
  - Early dysautonomia (impotence, orthostatic hypotension, diarrhoea-constipation, pupillary abnormalities)
  - Neuropathic pain
- Later other sensory modalities and motor involvement
- Cardiac arrhythmias, weight loss
- Frequent family history, high penetrance
- Relatively slow progression







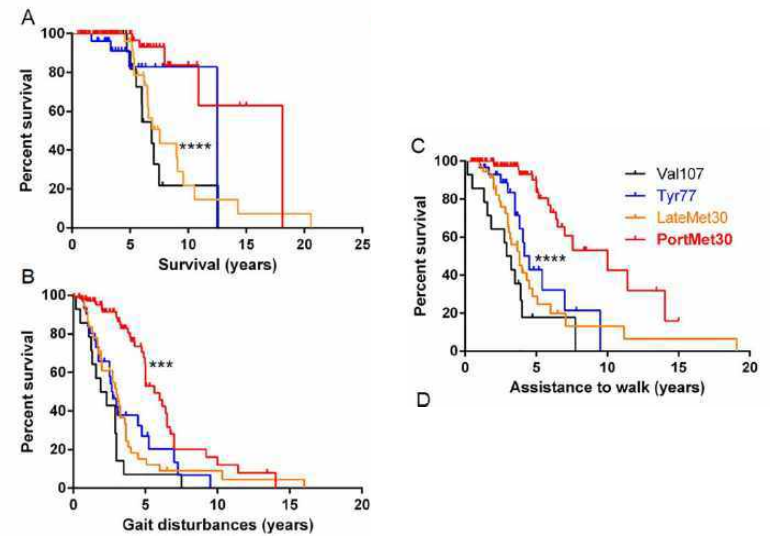
6



7

Genotype–Phenotype Correlation and Course of Transthyretin Familial Amyloid Polyneuropathies in France

Mariani et al ANN NEUROL 2015;78:901–916



8

hATTR in non-endemic countries

- ✓ **Late onset**, > 50 yrs (55-60 mean, onset > 80)
- ✓ Val30Met 25-30%, other mutations frequent
- ✓ Frequent **sporadic** presentation, incomplete penetrance
- ✓ **Male** predominance (2-3:1)
- ✓ **All fibre involvement** (all sensory modalities, early motor involvement)
- ✓ Subtle dysautonomia
- ✓ **Fast** progression
- ✓ Carpal tunnel syndrome – Fasciculations
- ✓ Atypical presentations: ataxic type, motor predominant (ALS-mimicking), upper limb predominance, cranial nerves
- ✓ Difficult diagnosis, frequent misdiagnosis, delay by 2-5 years

9

Comparison of clinical features between early-onset and late-onset hATTR-FAP
(modified from Sekijima et al. Orphanet Journal of Rare Diseases. 2018:13:6)

Clinical feature	Early onset	Late onset
Age of onset of symptoms	25-45	>=50
Penetrance	High	Low
Family history of ATTR-FAP	Common	Frequently absent
Mutation(s)	Val30Met	Val30Met + other mutations
Pattern of neuropathic symptoms	Small fibres first and more (>thermal-pain sensory loss)	All sensory modalities Early distal motor involv.
Autonomic dysfunction	Severe, life-threatening	Relatively mild
Heart	AV block requiring PM implantation	Frequent presence of cardiomegaly
Gender	Both genders affected	Male predominance
Course	Relatively slower	Fast
Amyloid type	B = full length TTR, high affinity for Congo Red	A = fragments + full length, low Congo Red affinity

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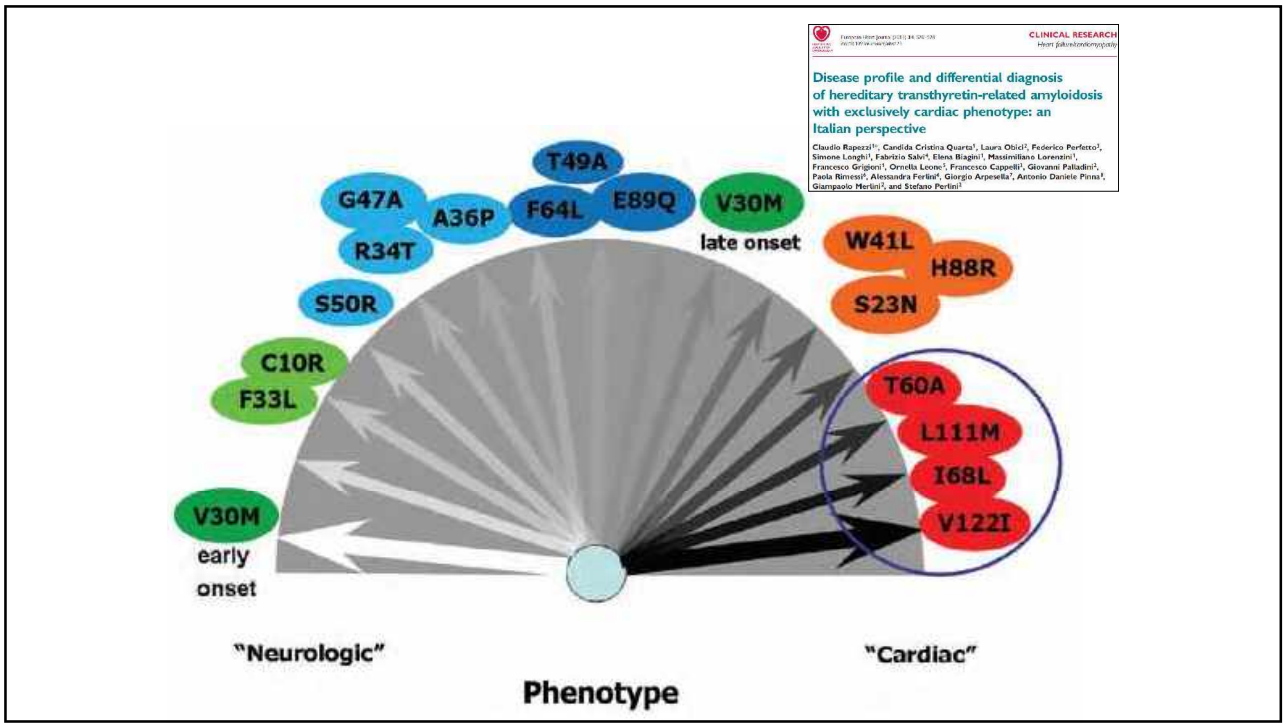
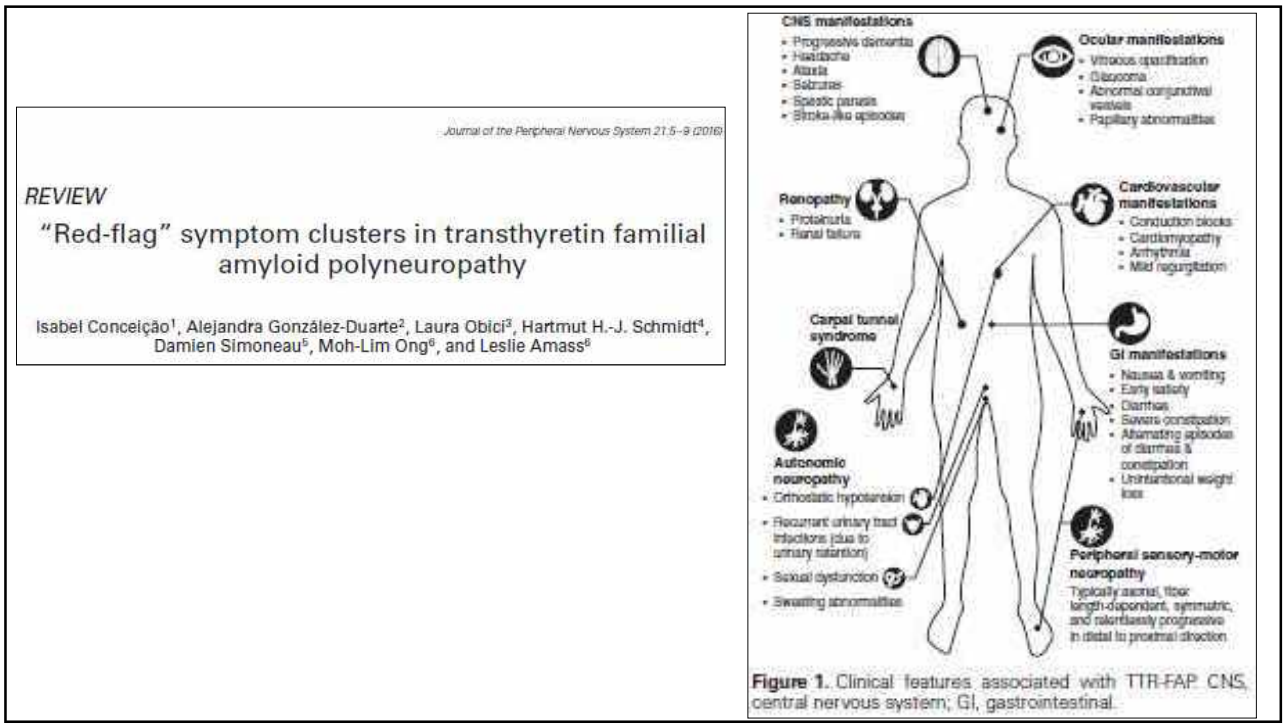

CLINICAL RESEARCH
Heart failure/cardiomyopathy
Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective
T49A
G47A
A36P
F64L
E89Q
V30M
late onset
R34T
S50R
W41L
H88R
S23N
C10R
F33L
T60A
L111M
I68L
V122I
V30M
early
onset
"Neurologic"
"Cardiac"
Phenotype

11


Journal of the Peripheral Nervous System 21:5–9 (2016)
REVIEW
"Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy
Isabel Conceição[1], Alejandra González-Duarte[2], Laura Obici[3], Hartmut H.-J. Schmidt[4], Damien Simoneau[5], Moh-Lim Ong[6], and Leslie Amass[6]
CNS manifestations
• Progressive dementia
• Headache
• Ataxia
• Seizures
• Spastic paresis
• Stroke-like episodes
Ocular manifestations
• Vitreous opacification
• Glaucoma
• Abnormal conjunctival vessels
• Pupillary abnormalities
Nephropathy
• Proteinuria
• Renal failure
Cardiovascular manifestations
• Conduction blocks
• Cardiomyopathy
• Arrhythmia
• Mild regurgitation
Carpal tunnel syndrome
GI manifestations
• Nausea & vomiting
• Early satiety
• Diarrhea
• Severe constipation
• Alternating episodes of diarrhea & constipation
• Unintentional weight loss
Autonomic neuropathy
• Orthostatic hypotension
• Recurrent urinary tract infections (due to urinary retention)
• Sexual dysfunction
• Sweating abnormalities
Peripheral sensory-motor neuropathy
Typically axonal, fiber length-dependent, symmetric, and relentlessly progressive in distal to proximal direction
Figure 1. Clinical features associated with TTR-FAP. CNS, central nervous system; GI, gastrointestinal.

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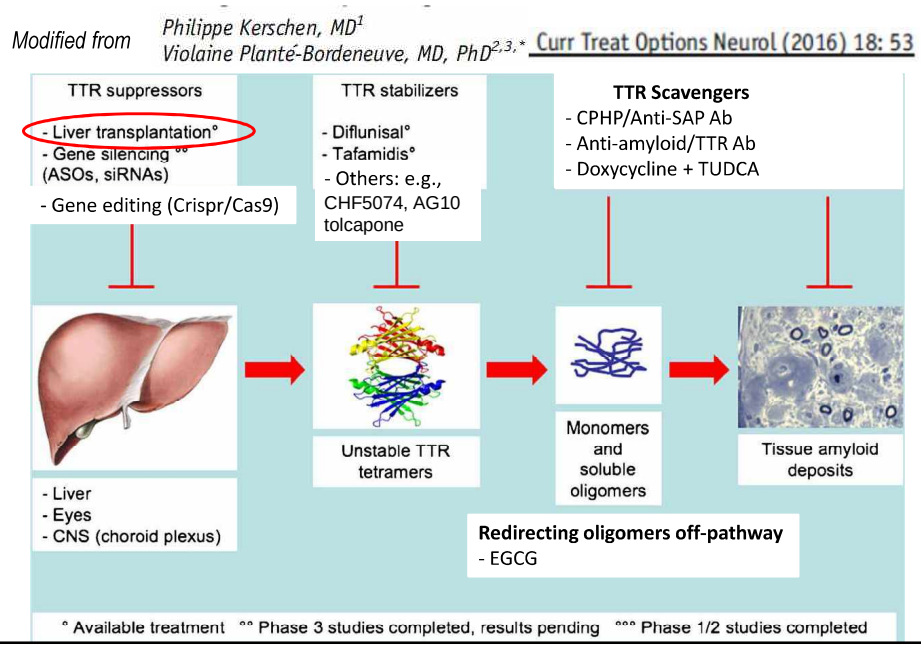
- FAP Stage 1: unimpaired ambulation
- FAP Stage 2: assistance with ambulation required
- FAP Stage 3: wheelchair-bound or bedridden

- PND I: sensory disturbances but preserved walking capability
- PND II: impaired walking capability but ability to walk without a stick or crutches
- PND IIIA: walking only with the help of one stick or crutch
- PND IIIB: walking with the help of two sticks or crutches
- PND IV: confined to a wheelchair or bedridden

Ando Y et al. *Orphanet Journal of Rare Diseases*. 2013;8:31.

13

Therapeutical approaches for Transthyretin-related Amyloidosis



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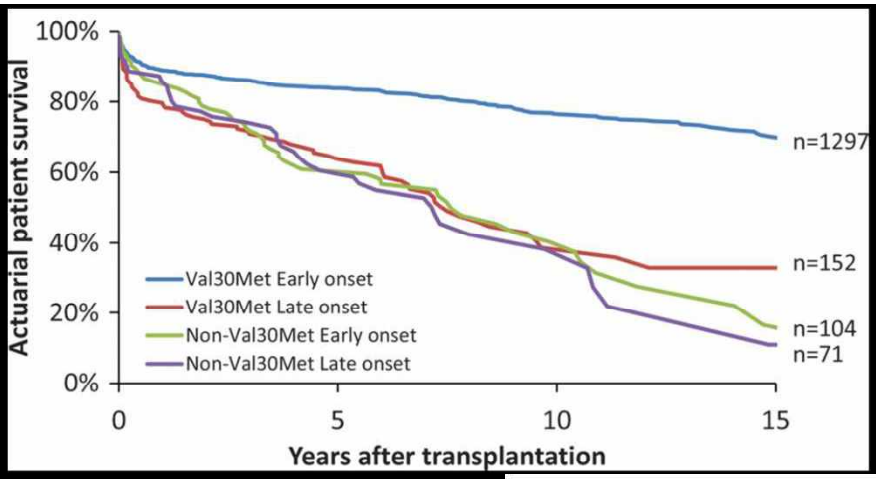


OLT: Patient survival between 1990-2010
TTR Val30Met vs non-TTR Val30Met
Early vs late onset of disease

Ericzon et al. Transplantation 2015; 99:1847-54

Carvalho et al. Liver Transplantation 2015; 21:282-92

TABLE 1. Factors to Consider for the Selection of OLT Candidates

Age < 50 years
Duration of symptoms < 7 years
Low polyneuropathy disability score
Modified body mass index ≥ 600 kg/m^2·g/L
No severe autonomic dysfunction
Absence of amyloid cardiomyopathy
No significant renal dysfunction

15

Cerebral amyloid angiopathy in posttransplant patients with hereditary ATTR amyloidosis

Neurology® 2016;87:773-781

Yoshiki Sekijima, MD, PhD
Masahide Yazaki, MD, PhD
Kenshiro Oguchi, MD, PhD
Naoki Ezawa, MD
Tsuneaki Yoshinaga, MD
Mitsunori Yamada, MD, PhD
Hiroyuki Yahikozawa, MD, PhD
Masahide Watanabe, MD, PhD
Fuyuki Kametani, PhD
Shu-ichi Ikeda, MD, PhD

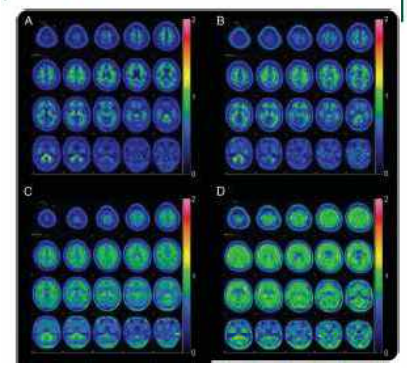
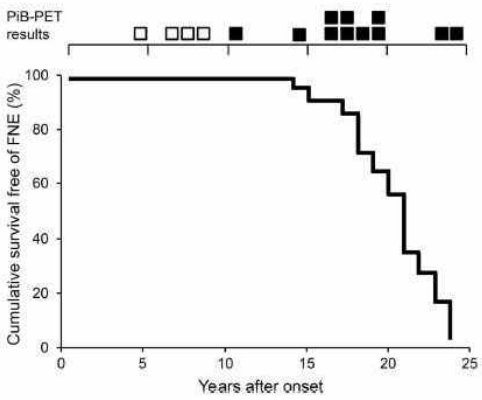


Figure 2 Prevalence of cerebral amyloid angiopathy in posttransplant patients with hereditary ATTR amyloidosis



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Impact of liver transplantation on the natural history of oculopathy in Portuguese patients with transthyretin (V30M) amyloidosis

João Melo Beirão[1,2,3], Jorge Malheiro[3], Carolina Lemos[4], Eduarda Matos[3], Idalina Beirão[2,3], Paulo Pinho-Costa[3,5], and Paulo Torres[1,3]

Amyloid, 2015; 22(1): 31–35

Table 2. Prevalence of ocular manifestations (global and both non-liver-transplanted (non-LT) and liver-transplanted (LT) patients).

	Total ($N=128$)	Non-LT ($N=64$)	LT ($N=64$)	p Values
ACV, n (%)	22 (17.2%)	12 (18.8%)	10 (15.5%)	$p=0.639$
Positive Schirmer test, n (%)	88 (68.8%)	52 (81.2%)	36 (56.2%)	$p=0.002$
Positive TBUT, n (%)	106 (82.8%)	54 (84.4%)	52 (81.2%)	$p=0.639$
Amyloid, Iris, n (%)	31 (24.2%)	14 (21.9%)	17 (26.6%)	$p=0.536$
Scalloped Iris, n (%)	22 (17.2%)	12 (18.8%)	10 (15.6%)	$p=0.639$
Amyloid, Lens, n (%)	26 (20.3%)	10 (15.6%)	16 (25.0%)	$p=0.187$
Amyloid, vitreous, n (%)	17 (13.3%)	7 (10.9%)	10 (15.6%)	$p=0.435$
Retinal angiopathy, n (%)	1 (0.8%)	1 (1.6%)	0 (0%)	$p=0.315$
Glaucoma, n (%)	11 (8.6%)	5 (7.8%)	6 (9.4%)	$p=0.752$

Conclusions: Ocular manifestations of FAP were not influenced by liver transplantation in a meaningful way. Both transplanted and non-transplanted FAP patients need similar regular follow-up due to long-term risk of serious ocular disease.

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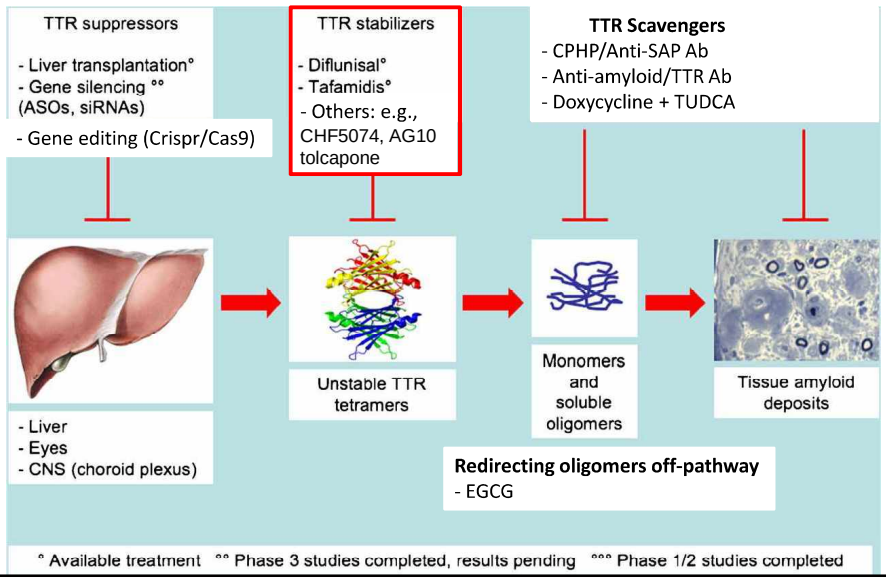
Therapeutical approaches for Transthyretin-related Amyloidosis

Modified from *Philippe Kerschen, MD*[1] *Violaine Planté-Bordeneuve, MD, PhD*[2,3,*] Curr Treat Options Neurol (2016) 18: 53



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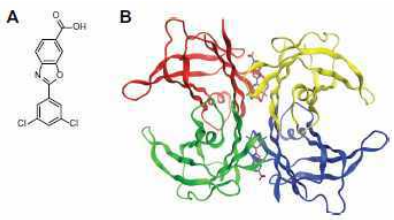
Tafamidis meglumine



Approved in 24 countries

20 mg/day

In Europe for adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment; in Japan for all stages

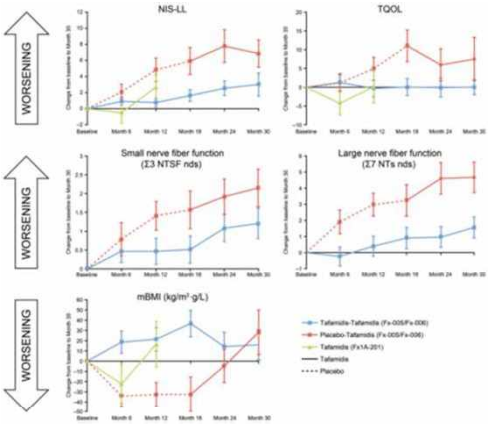
80 mg/day effective for Cardiomyopathy (NEJM 2018)

Neurol Ther (2016) 5:1–25
DOI 10.1007/s40120-016-0040-x

REVIEW

Mechanism of Action and Clinical Application of Tafamidis in Hereditary Transthyretin Amyloidosis

Teresa Coelho · Giampaolo Merlini · Christine E. Bulawa · James A. Fleming · Daniel P. Judge · Jeffery W. Kelly · Mathew S. Maurer · Violaine Planté-Bordeneuve · Richard Labaudinière · Rajiv Mundayat · Steve Riley · Ilise Lombardo · Pedro Huertas



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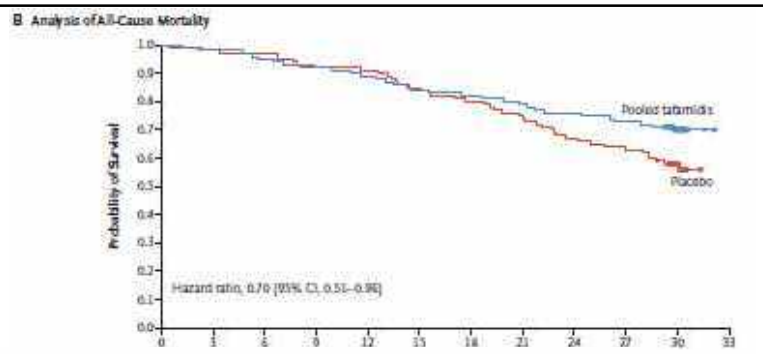
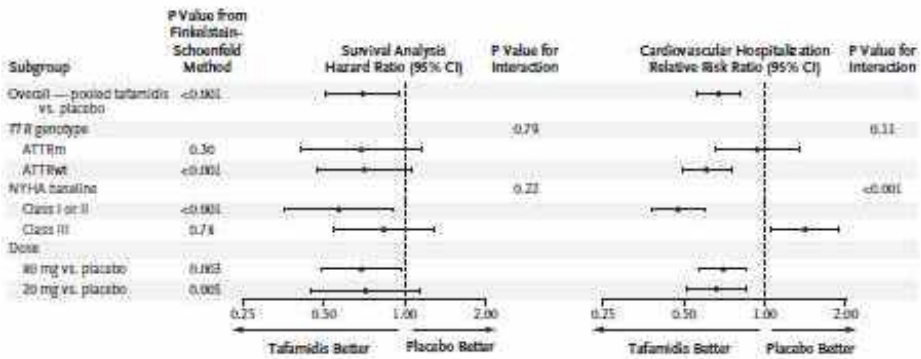
The NEW ENGLAND JOURNAL of MEDICINE
SEPTEMBER 13, 2018

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcio Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michele Stewart, Ph.D., Maria B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators





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Authors	Journal	Population	Trial	N°	Outcome
Berk et al	JAMA 2013	Any type	24 months double blind placebo-controlled	130 pts	Slower progression of NIS+7, NIS, NIS-LL, Kumamoto. Better SF36. No mBMI. Overall well tolerated

DIFLUNISAL

Nonsteroidal anti-inflammatory agent

Dosage = 250 mg x 2/day

Not licensed with few exceptions, available as galenic compound in some countries (off-label treatment)

Table 3. Multiple Imputation Analysis of Primary (NIS+7) and Secondary Outcomes[a]

Outcomes	Mean (95% CI) Placebo Change From Baseline	Diflunisal Change From Baseline	Difference, Placebo–Diflunisal	P Value
NIS+7 score				
At 1 year	12.5 (8.6 to 16.4)	6.4 (3.1 to 9.6)	6.1 (1.1 to 11.1)	.02
At 2 years	25.0 (18.4 to 31.6)	8.7 (3.3 to 14.1)	16.3 (8.1 to 24.5)	<.001
NIS score				
At 1 year	10.1 (6.9 to 13.3)	4.2 (1.5 to 7.0)	5.9 (1.8 to 10.0)	.005
At 2 years	22.8 (17.2 to 28.4)	6.7 (1.9 to 11.4)	16.1 (9.0 to 23.2)	<.001
NIS-LL score				
At 1 year	6.0 (3.9 to 8.2)	3.3 (1.4 to 5.1)	2.8 (0.0 to 5.6)	.05
At 2 years	12.1 (8.7 to 15.5)	3.8 (1.0 to 6.7)	8.2 (4.0 to 12.5)	<.001
Kumamoto score				
At 1 year	4.1 (1.9 to 6.4)	1.9 (0.0 to 3.7)	2.3 (−0.6 to 5.2)	.12
At 2 years	8.1 (5.7 to 10.6)	3.2 (1.1 to 5.3)	4.9 (1.7 to 8.1)	.003
Modified BMI[b]				
At 1 year	−40.3 (−75.4 to −5.2)	−19.7 (−54.1 to 14.7)	−20.6 (−69 to 27.9)	.41
At 2 years	−65.1 (−107.4 to −22.7)	−35.2 (−73.6 to 3.3)	−29.9 (−85.7 to 25.9)	.29
SF-36 physical component score				
At 1 year	−1.9 (−3.8 to −0.1)	0.8 (−0.9 to 2.5)	−2.8 (−5.2 to −0.3)	.03
At 2 years	−4.9 (−7.6 to −2.2)	1.5 (−0.8 to 3.7)	−6.4 (−9.8 to −2.9)	<.001
SF-36 mental component score				
At 1 year	0.6 (−1.7 to 3.0)	2.3 (0.1 to 4.5)	−1.7 (−4.9 to 1.5)	.30
At 2 years	−1.1 (−4.3 to 2.0)	3.7 (1.0 to 6.4)	−4.9 (−9.0 to −0.7)	.02

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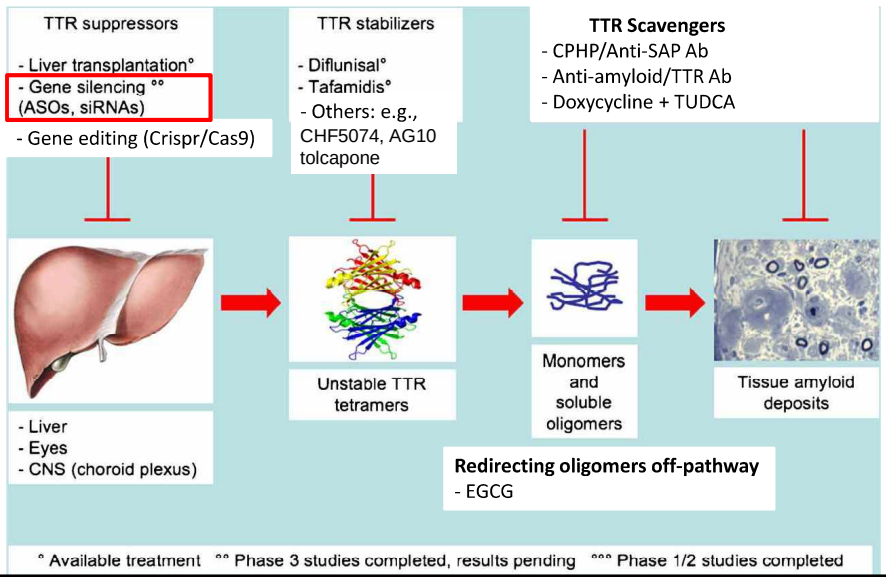
Therapeutical approaches for Transthyretin-related Amyloidosis

Modified from *Philippe Kerschen, MD*[1] *Violaine Planté-Bordeneuve, MD, PhD*[2,3,*] Curr Treat Options Neurol (2016) 18: 53



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

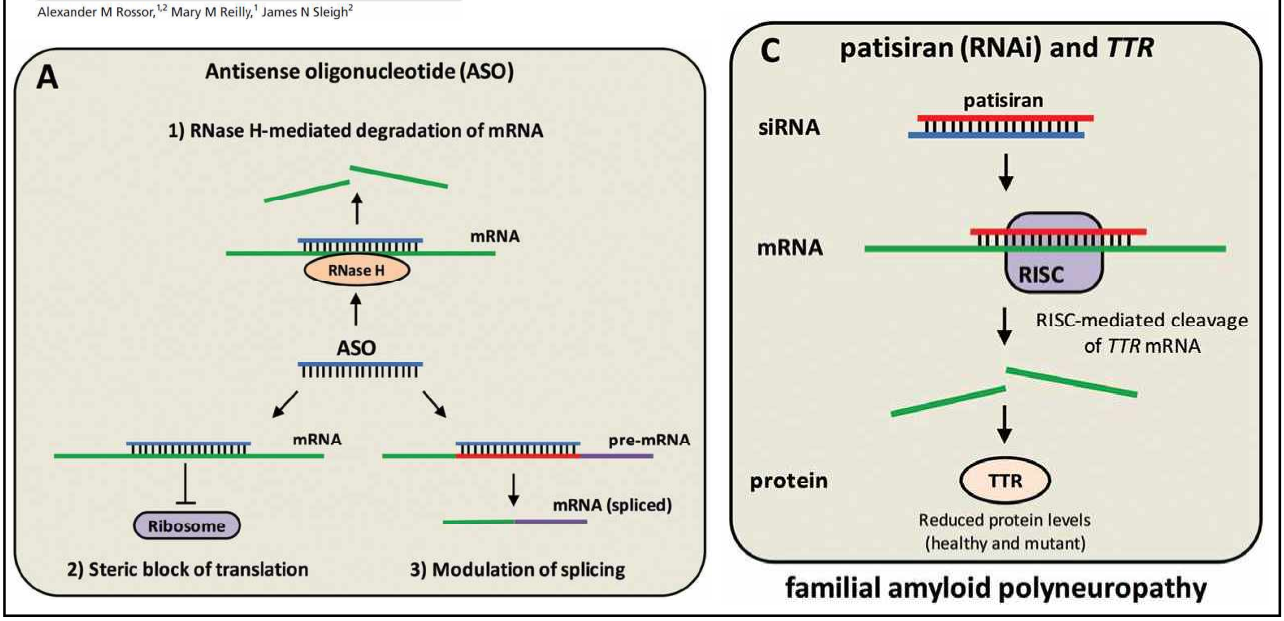
D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

23

Antisense oligonucleotides and other genetic therapies made simple

Alexander M Rossor,[1,2] Mary M Reilly,[1] James N Sleigh[2]

Rossor AM, *et al*. *Pract Neurol* 2018;**18**:126–131.



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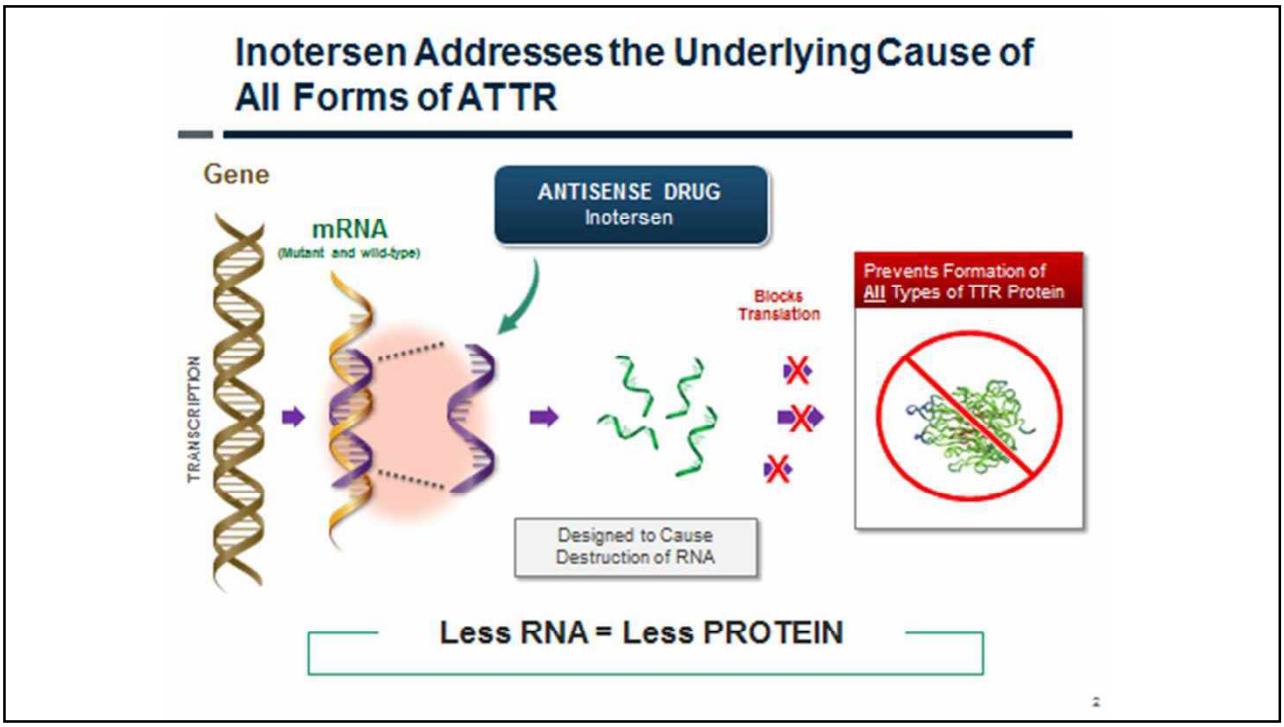
Inotersen Addresses the Underlying Cause of All Forms of ATTR
Gene
mRNA
(Mutant and wild-type)
TRANSCRIPTION
ANTISENSE DRUG
Inotersen
Blocks Translation
Prevents Formation of All Types of TTR Protein
Designed to Cause Destruction of RNA
Less RNA = Less PROTEIN

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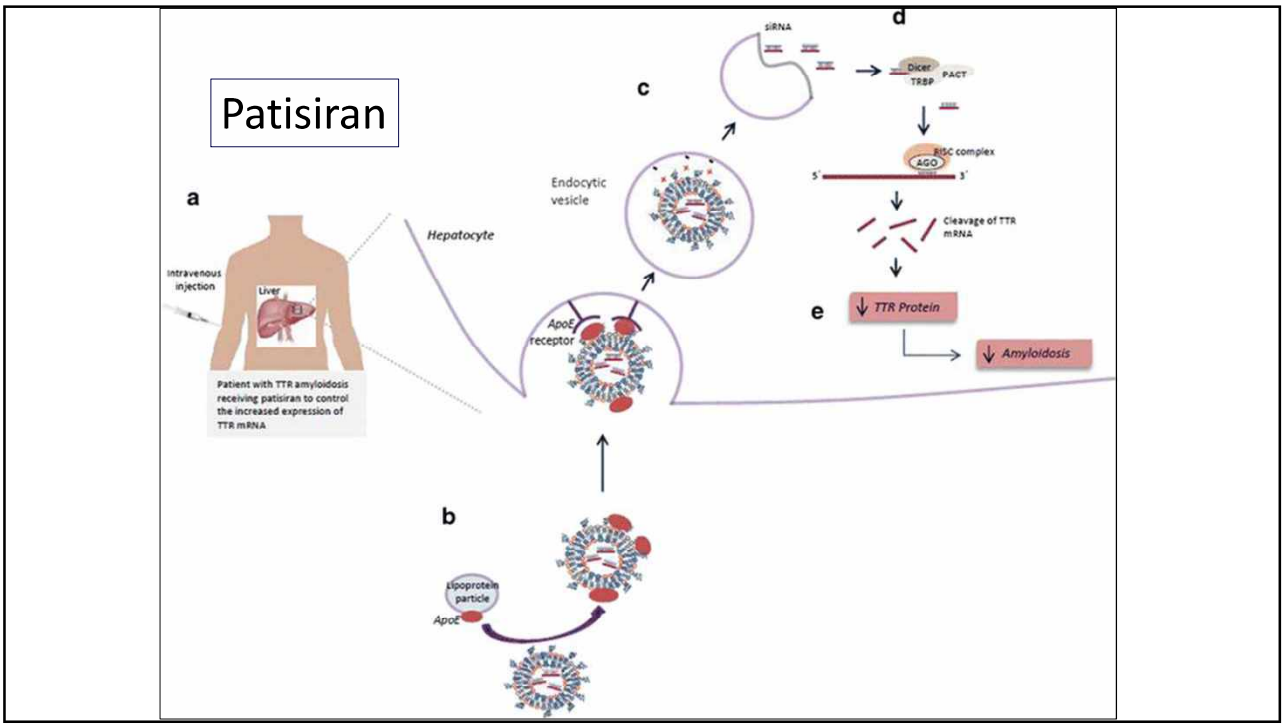
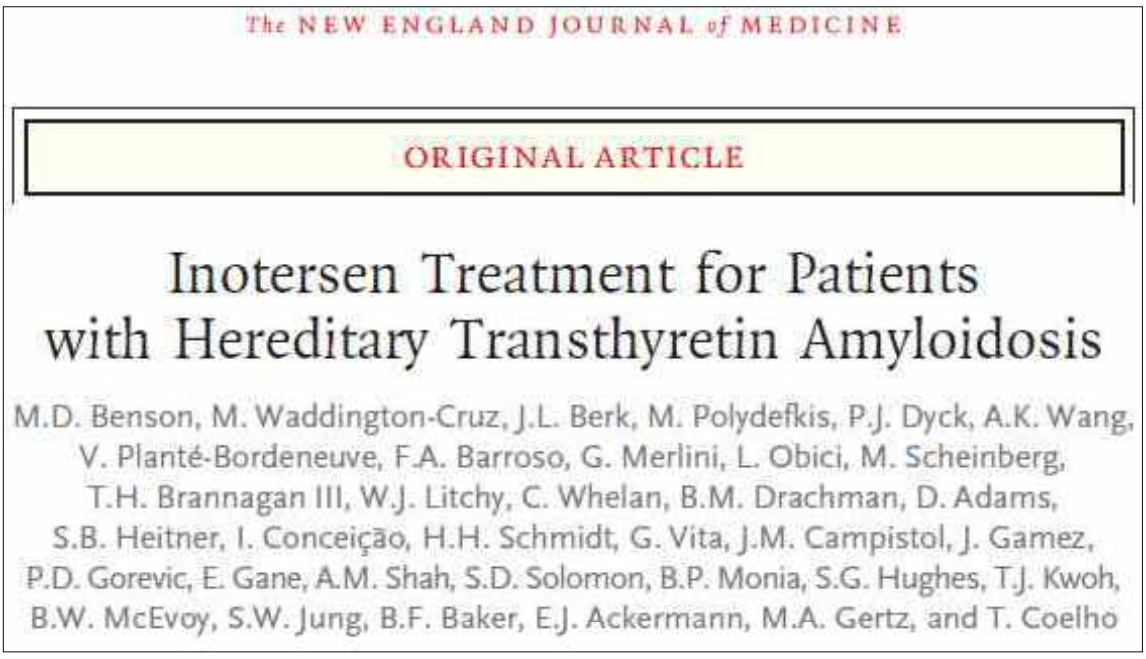

Patisiran
a
Intravenous injection
Liver
Patient with TTR amyloidosis receiving patisiran to control the increased expression of TTR mRNA
Hepatocyte
Endocytic vesicle
ApoE receptor
b
Lipoprotein particle
ApoE
c
siRNA
d
Dicer
TRBP
PACT
RISC complex
AGO
Cleavage of TTR mRNA
e
TTR Protein
Amyloidosis

26

Compound - Study	Inotersen – Neuro-TTR (Ionis-Akcea)	Patisiran – Apollo (Alnylam)
	Anti-Sense Oligonucleotides	RNAi lipid nanoparticles
Mechanism	Bind to wild type and mutated TTR mRNA	
TTR reduction	75-79%	84%; 87.8% mean max serum reduction
Route	Subcutaneously - once a week	Intravenously - every 3 weeks
Study Phase	Phase 3 completed, OLE ongoing	Phase 3 completed, OLE ongoing
Ratio treated:placebo	2:1	2:1
Duration	15 months	18 months
Primary Endpoints	Norfolk QoL, mNIS+7	mNIS+7
Participants	172 randomised, 150 completed 17 treated dropped out	225 randomised 193 completed 29 placebo dropped out
Outcome	Norfolk = 12 points difference at 15 months; 50% stabilised or improved	Norfolk = 21.1 points difference at 18 months; 51.4% "improved"
	mNIS+7 = 20 points difference at 15 months; 36% stabilised or improved	mNIS+7 = 33.99 point difference at 18 months; 56% "improved"
	Independent from disease stage, presence of cardiomyopathy, type of mutation	Independent from disease stage, presence of cardiomyopathy, type of mutation
Side effects	Thrombocytopenia (4 cases, 1 death); 6 renal problems	Infusion related reactions, peripheral edema

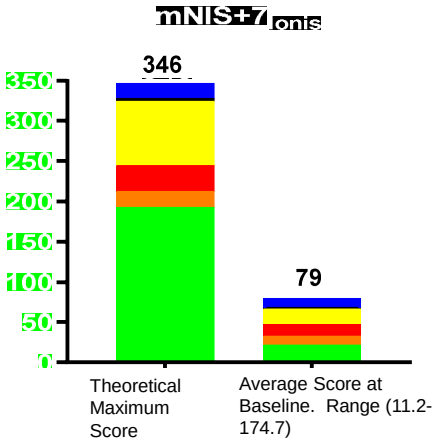
27

27



28

mNIS+7 Composite Score Measures Muscle Strength, Reflex, Sensation and Autonomic Function



- Nerve Conduction
- HRDB - Autonomic
- Touch-Pressure – Sensation Large Fiber (full body)
- Heat-Pain - Sensation Small Fiber (full body)

modified+7 (4 subcomponents)

- Sensation – Big toe and index finger
- Reflexes
- Muscle Weakness - Upper and Lower Limbs
- Muscle Weakness - Cranial Nerves

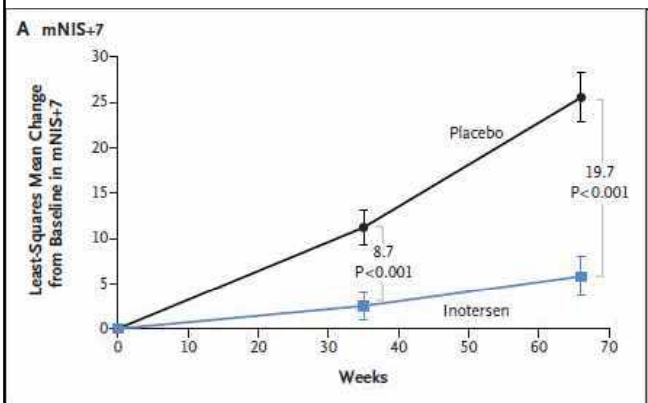
NIS (4 subcomponents)

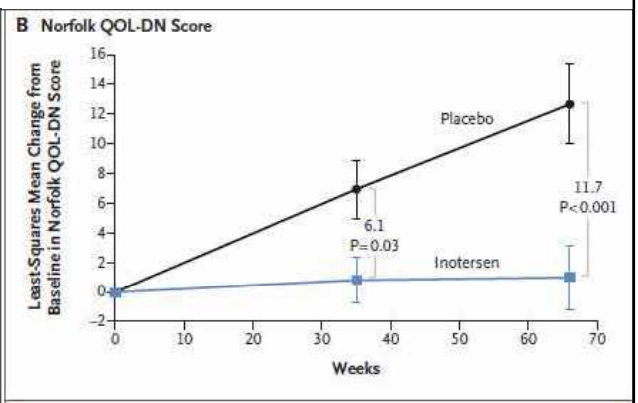
1. *Dyck, et al. Muscle and Nerve. 2017*

29

29

Figure 2. Change from Baseline in Primary End Points.





riod. Further analysis of patients who completed the intervention period showed that 36% of the patients in the inotersen group had an improvement (no increase from baseline) in the mNIS+7 and 50% had an improvement in the Norfolk QOL-DN score (Table S5 in the Supplementary Appendix).

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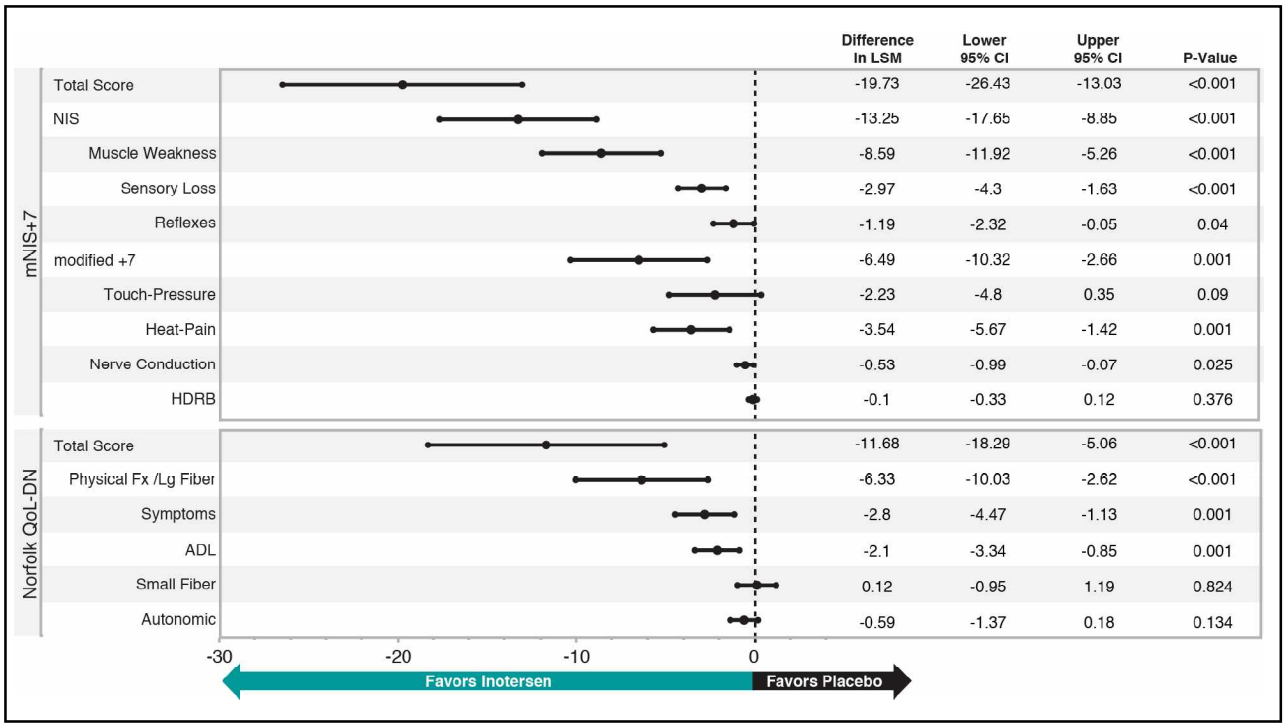
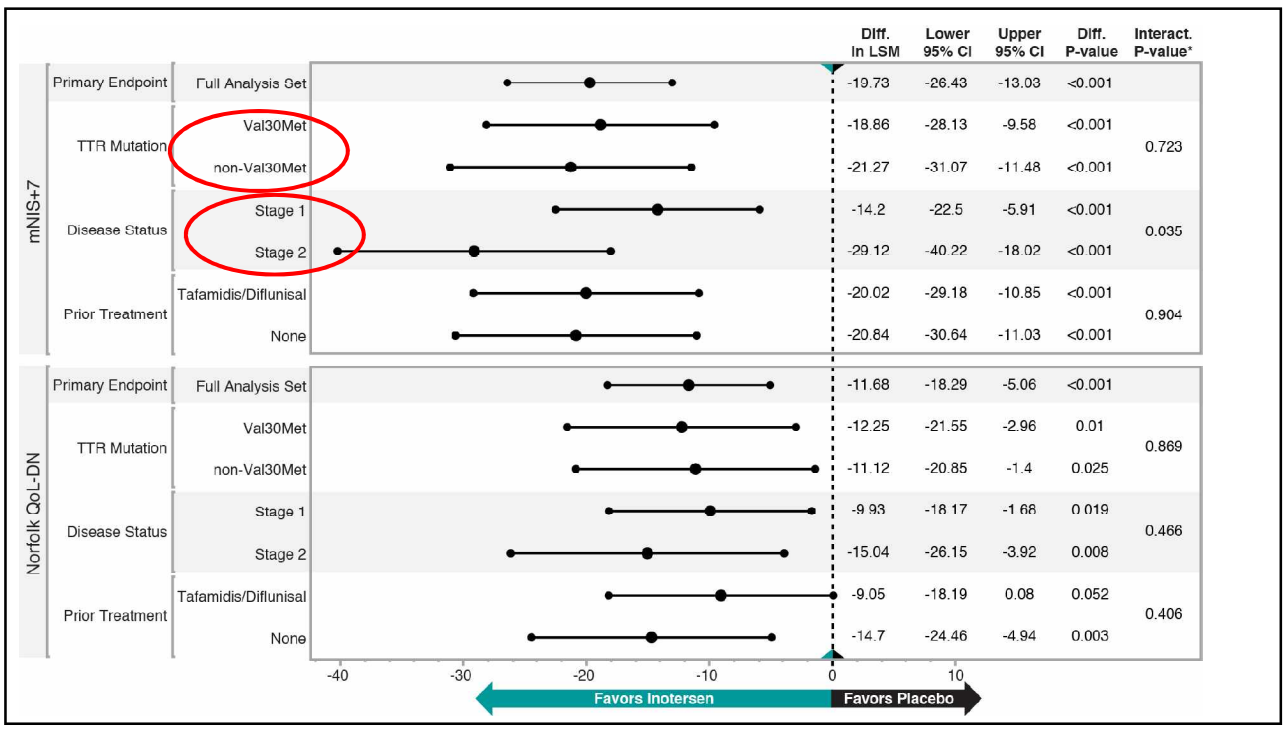
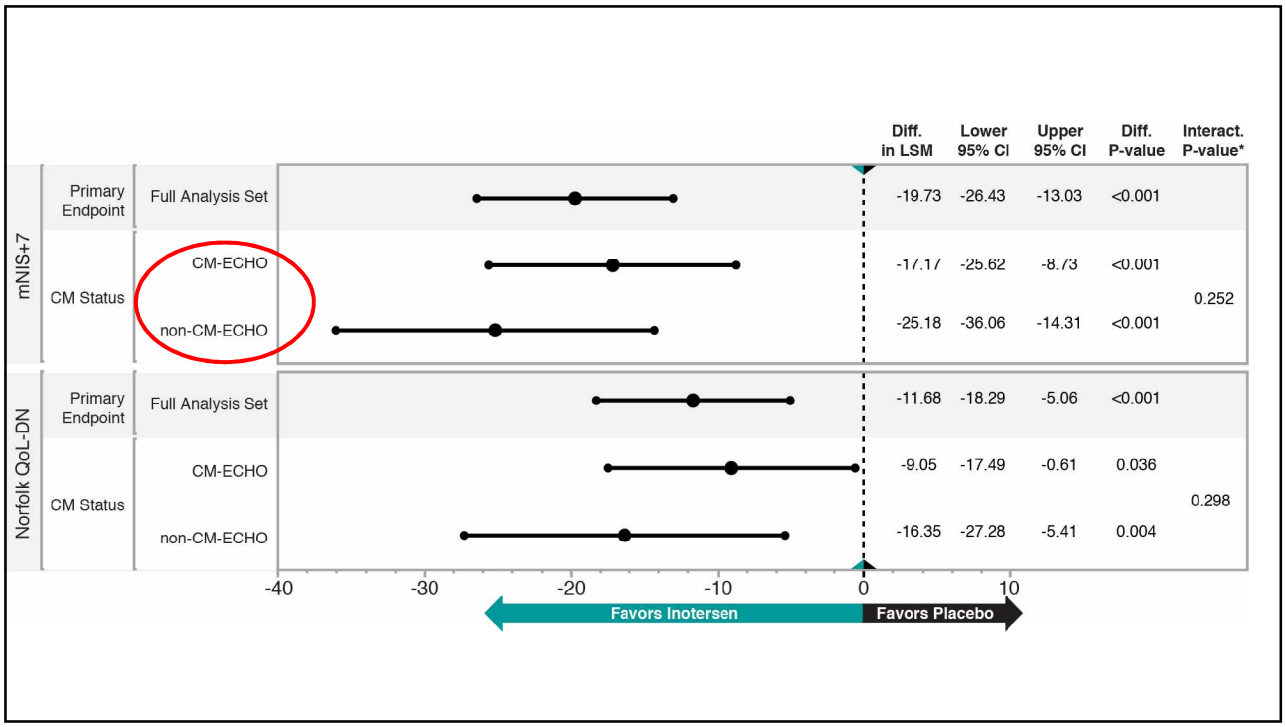

Difference In LSM
Lower 95% CI
Upper 95% CI
P-Value
mNIS+7
Total Score -19.73 -26.43 -13.03 <0.001
NIS -13.25 -17.65 -8.85 <0.001
Muscle Weakness -8.59 -11.92 -5.26 <0.001
Sensory Loss -2.97 -4.3 -1.63 <0.001
Reflexes -1.19 -2.32 -0.05 0.04
modified +7 -6.49 -10.32 -2.66 0.001
Touch-Pressure -2.23 -4.8 0.35 0.09
Heat-Pain -3.54 -5.67 -1.42 0.001
Nerve Conduction -0.53 -0.99 -0.07 0.025
HDRB -0.1 -0.33 0.12 0.376
Norfolk QoL-DN
Total Score -11.68 -18.29 -5.06 <0.001
Physical Fx /Lg Fiber -6.33 -10.03 -2.62 <0.001
Symptoms -2.8 -4.47 -1.13 0.001
ADL -2.1 -3.34 -0.85 0.001
Small Fiber 0.12 -0.95 1.19 0.824
Autonomic -0.59 -1.37 0.18 0.134
-30
-20
-10
0
Favors Inotersen
Favors Placebo

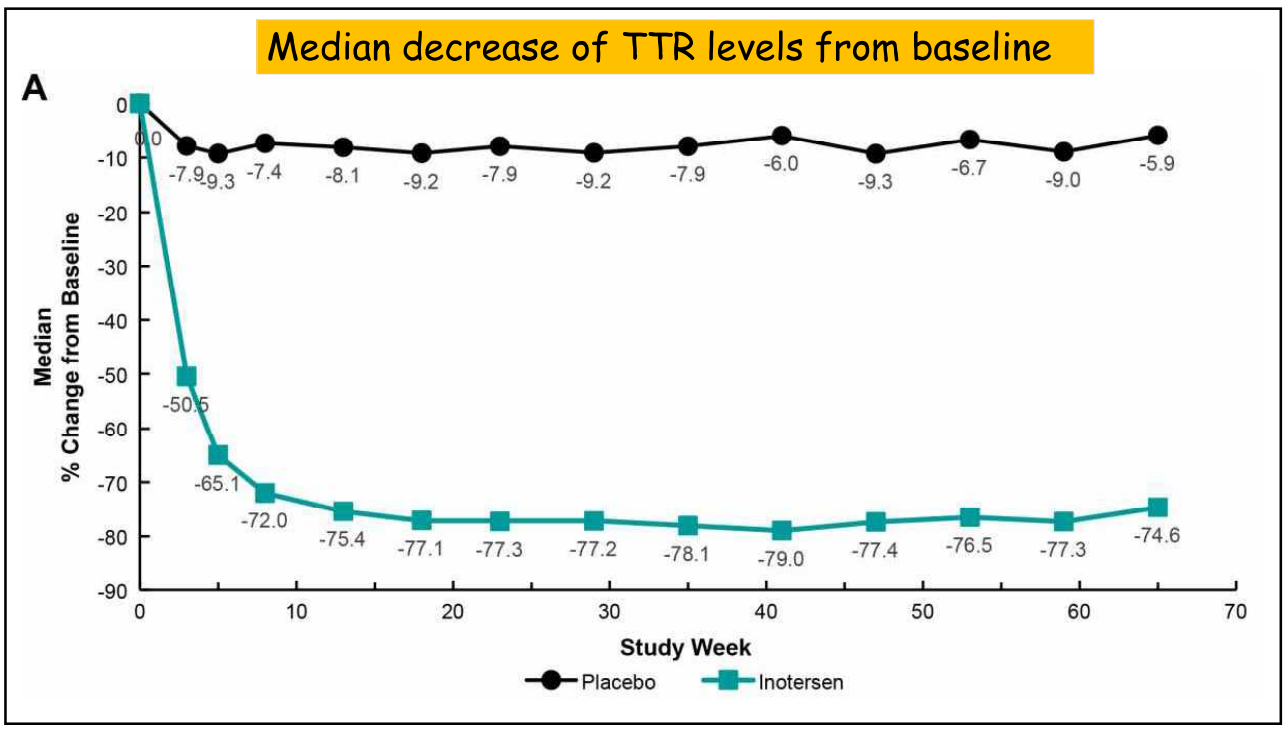
31


Diff. In LSM
Lower 95% CI
Upper 95% CI
Diff. P-value
Interact. P-value*
mNIS+7
Primary Endpoint Full Analysis Set -19.73 -26.43 -13.03 <0.001
TTR Mutation
Val30Met -18.86 -28.13 -9.58 <0.001 0.723
non-Val30Met -21.27 -31.07 -11.48 <0.001
Disease Status
Stage 1 -14.2 -22.5 -5.91 <0.001 0.035
Stage 2 -29.12 -40.22 -18.02 <0.001
Prior Treatment
Tafamidis/Diflunisal -20.02 -29.18 -10.85 <0.001 0.904
None -20.84 -30.64 -11.03 <0.001
Norfolk QoL-DN
Primary Endpoint Full Analysis Set -11.68 -18.29 -5.06 <0.001
TTR Mutation
Val30Met -12.25 -21.55 -2.96 0.01 0.869
non-Val30Met -11.12 -20.85 -1.4 0.025
Disease Status
Stage 1 -9.93 -18.17 -1.68 0.019 0.466
Stage 2 -15.04 -26.15 -3.92 0.008
Prior Treatment
Tafamidis/Diflunisal -9.05 -18.19 0.08 0.052 0.406
None -14.7 -24.46 -4.94 0.003
-40
-30
-20
-10
0
10
Favors Inotersen
Favors Placebo

32

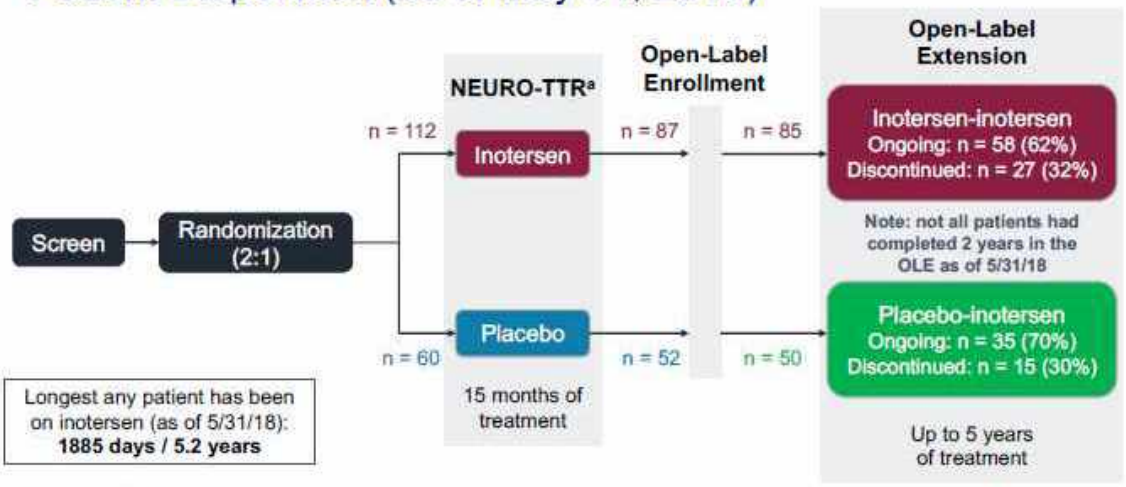

Diff. in LSM
Lower 95% CI
Upper 95% CI
Diff. P-value
Interact. P-value*
mNIS+7
Primary Endpoint
Full Analysis Set
-19.73
-26.43
-13.03
<0.001
CM Status
CM-ECHO
-17.17
-25.62
-8.73
<0.001
0.252
non-CM-ECHO
-25.18
-36.06
-14.31
<0.001
Norfolk QoL-DN
Primary Endpoint
Full Analysis Set
-11.68
-18.29
-5.06
<0.001
CM Status
CM-ECHO
-9.05
-17.49
-0.61
0.036
0.298
non-CM-ECHO
-16.35
-27.28
-5.41
0.004
-40
-30
-20
-10
0
10
Favors Inotersen
Favors Placebo

33


Median decrease of TTR levels from baseline
A
Median % Change from Baseline
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
0.0
-7.9
-9.3
-7.4
-8.1
-9.2
-7.9
-9.2
-7.9
-6.0
-9.3
-6.7
-9.0
-5.9
-50.5
-65.1
-72.0
-75.4
-77.1
-77.3
-77.2
-78.1
-79.0
-77.4
-76.5
-77.3
-74.6
0
10
20
30
40
50
60
70
Study Week
Placebo
Inotersen

34

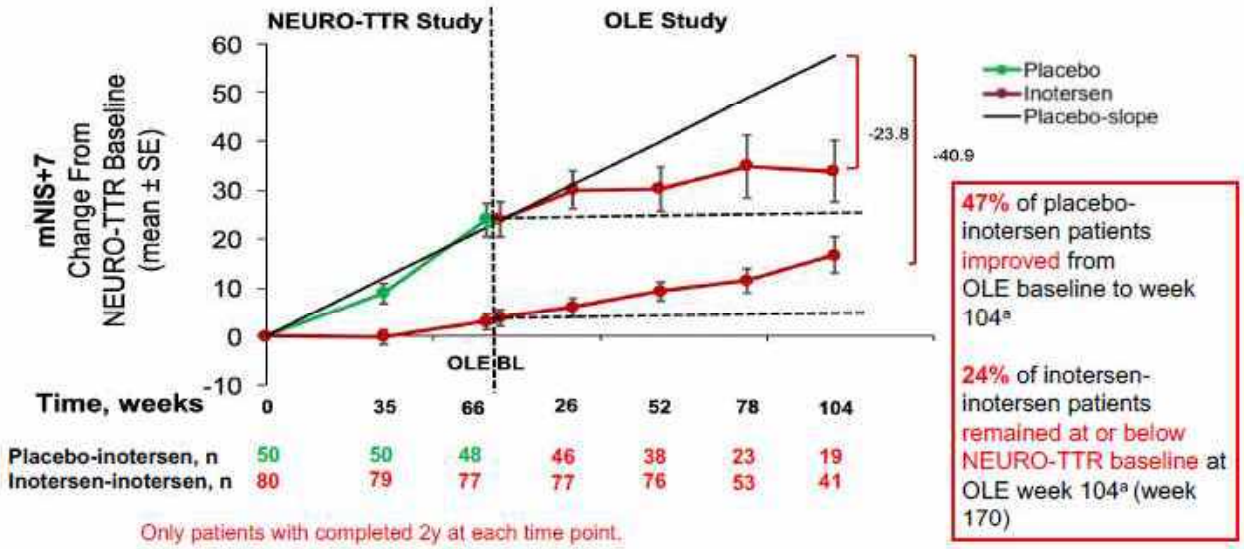
NEURO-TTR and OLE Study Design and Patient Disposition (as of May 31, 2018)



OLE, open-label extension; TTR, transthyretin.
[a]The n values for NEURO-TTR represent the number of patients randomized and treated. Overall, 139 patients (80.3%) completed the NEURO-TTR study, and >95% of patients who completed dosing participated in the OLE.
Benson MD et al. *N Engl J Med*. 2018;379(1):22-31.
Brannagan et al. ASH 2018 Oral presentation

35

Patients Who Switched From Placebo to Inotersen Demonstrated Sustained Improvement in Neuropathy Progression



BL, baseline; mNIS+7, modified Neuropathy Impairment Score +7 neurophysiologic tests composite score; OLE, open-label extension; SE, standard error.

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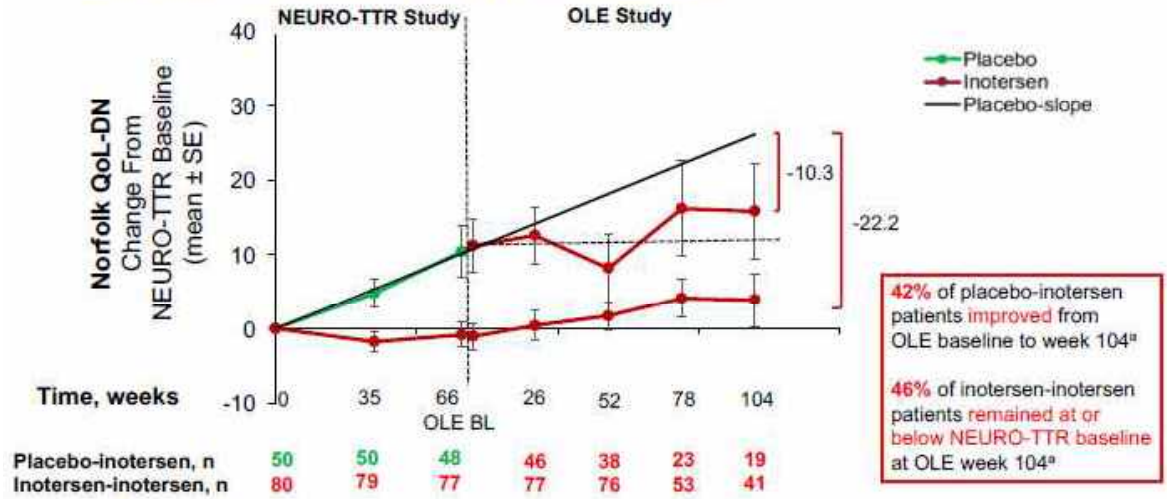
Patients Who Switched From Placebo to Inotersen Demonstrated Stabilization of Neuropathy-Related QoL



42% of placebo-inotersen patients improved from OLE baseline to week 104[a]

46% of inotersen-inotersen patients remained at or below NEURO-TTR baseline at OLE week 104[a]

Analysis include only patients who completed 2-y FwUp at cut off date.

BL, baseline; Norfolk QoL-DN, Norfolk Quality of Life–Diabetic Neuropathy questionnaire total score; OLE, open-label extension; QoL, quality of life; SE, standard error.

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The NEW ENGLAND JOURNAL of MEDICINE

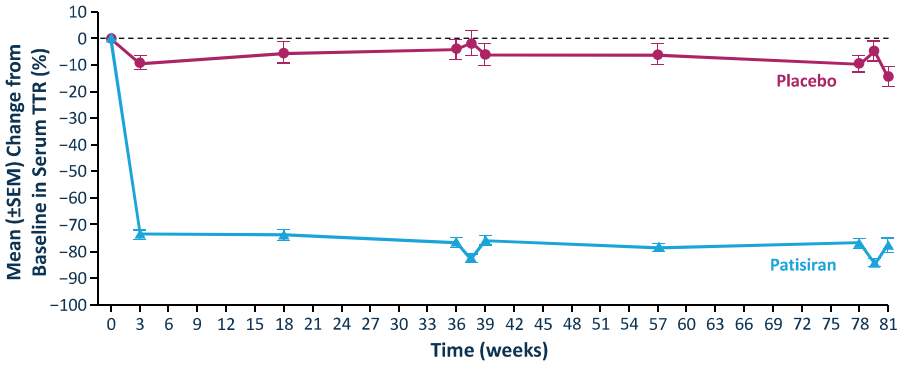
ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

38

Reduction in Serum TTR Levels Was Rapid and Sustained over 18 Months in the APOLLO Study[1,2]



- Mean reduction of serum TTR level after 18 months' patisiran treatment was **84%**[2]

Patisiran rapidly reduced serum TTR levels compared with baseline and placebo, and sustained the reduction over 18 months

1. Adams et al. *N Engl J Med* 2018;379:11–21. From N Engl J Med, Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Planté-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH 3rd, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB, Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis, 379, 11–21 Copyright © (2018) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society; 2. European Medicines Agency. Summary of product characteristics: patisiran. 2018. Available from: https://www.ema.europa.eu/documents/product-information/onpattro-epar-product-information_en.pdf (accessed June 2019)

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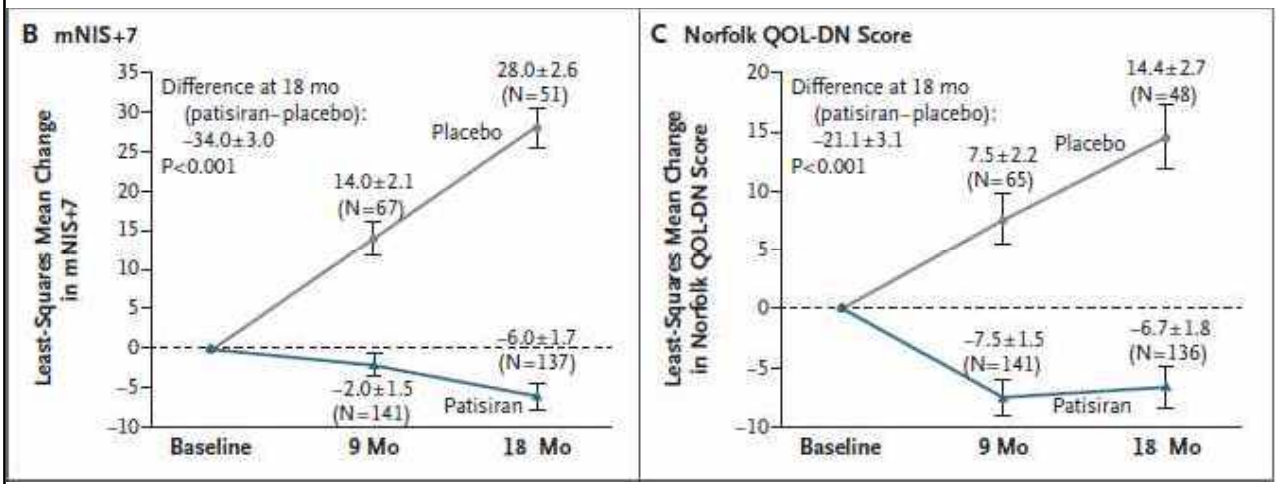
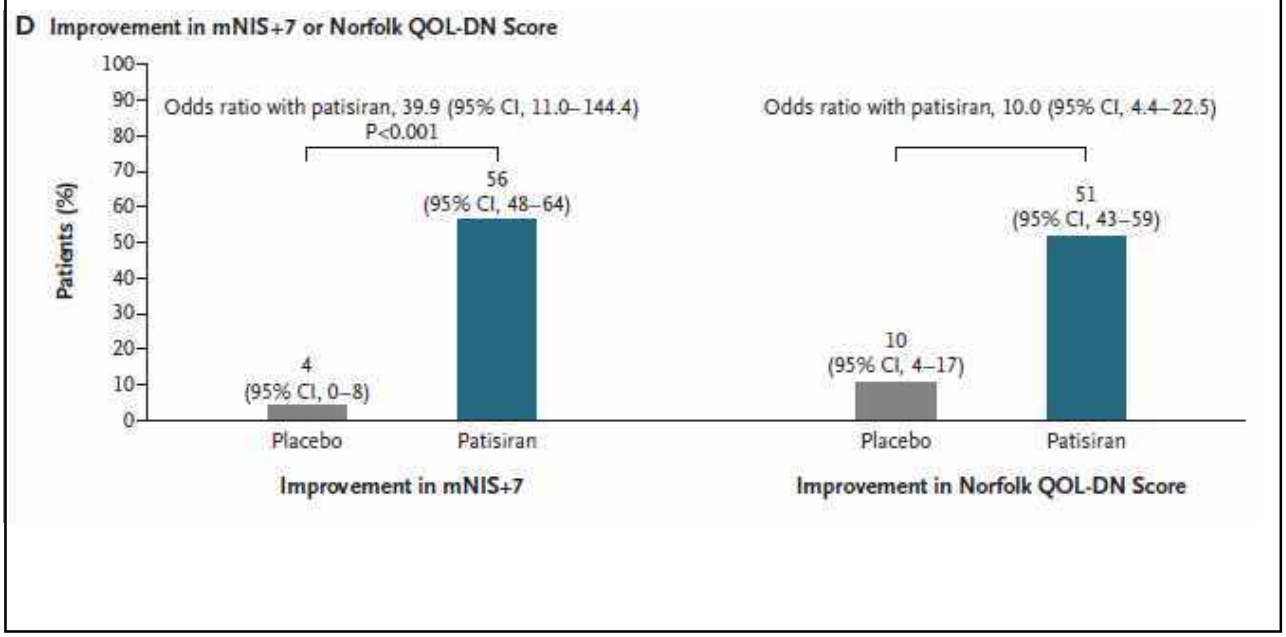
Figure 2. Comparisons of Changes between the Patisiran Group and the Placebo Group over Time.



40

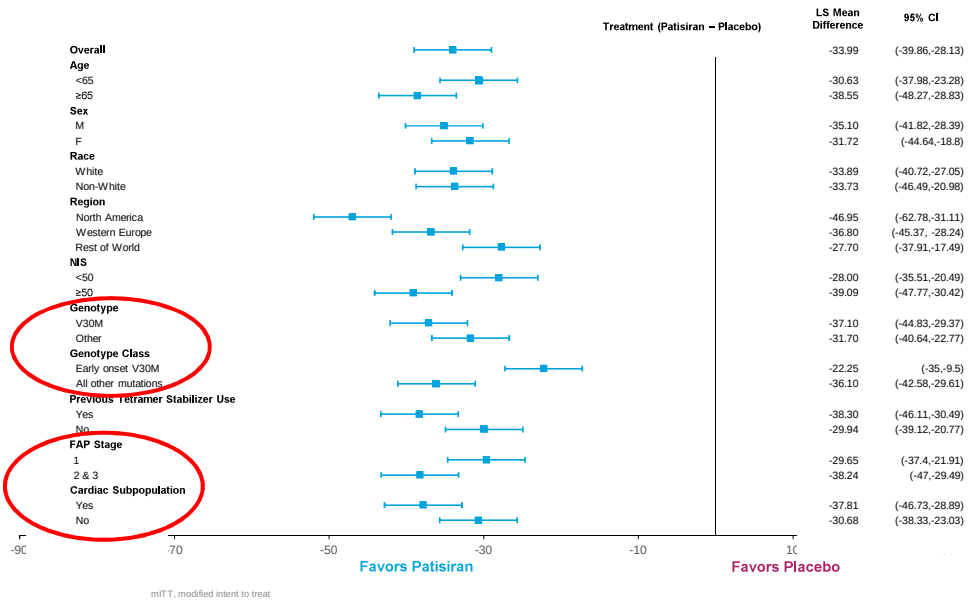
Figure 2. Comparisons of Changes between the Patisiran Group and the Placebo Group over Time.



41

Patisiran Phase 3 APOLLO Study Results

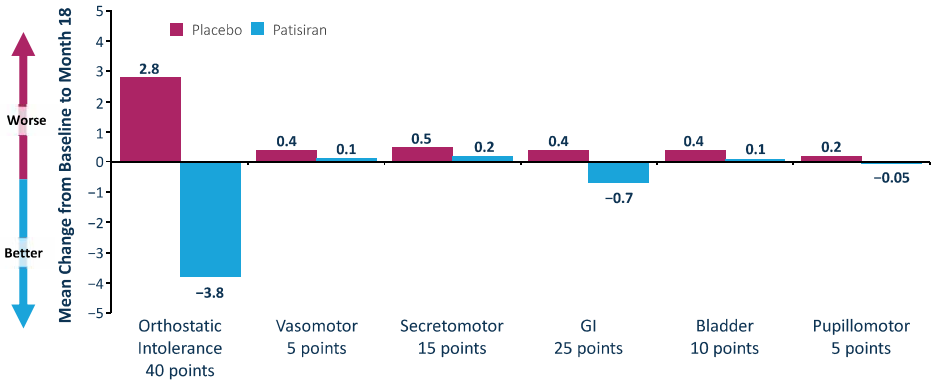
mNIS+7: Change from Baseline to Month 18 in Subgroups



42

Autonomic Effect: Patisiran Improved/Stabilized Multiple Autonomic Symptoms from Baseline to Month 18 in the APOLLO Study

Mean Change from Baseline to Month 18 in Domains of COMPASS-31



Patisiran also improved Norfolk QOL-DN autonomic domain (including questions on vomiting, diarrhea, and dizziness/fainting) compared with placebo at 18 months

Mauermann et al. *International Congress on Neuromuscular Disease (ICNMD) Congress* 2018

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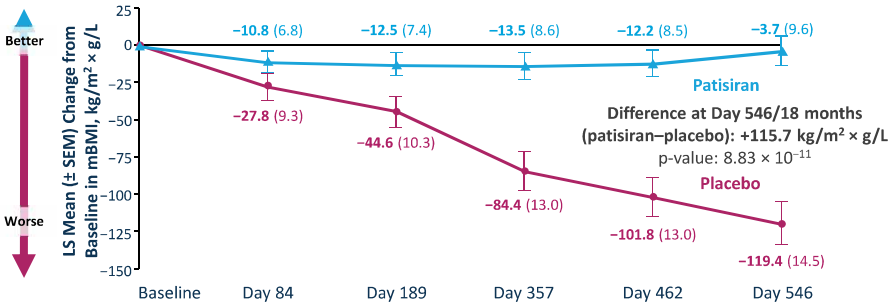
Patisiran Improved mBMI Relative to Baseline in the APOLLO Study



- At 18 months, **41% (patisiran)** vs **6.5% (placebo)** demonstrated improvement from baseline in mBMI

Patients receiving patisiran maintained their mBMI over 18 months, whereas mBMI declined significantly in those receiving placebo

Obici et al. *European Academy of Neurology (EAN) Congress* 2018

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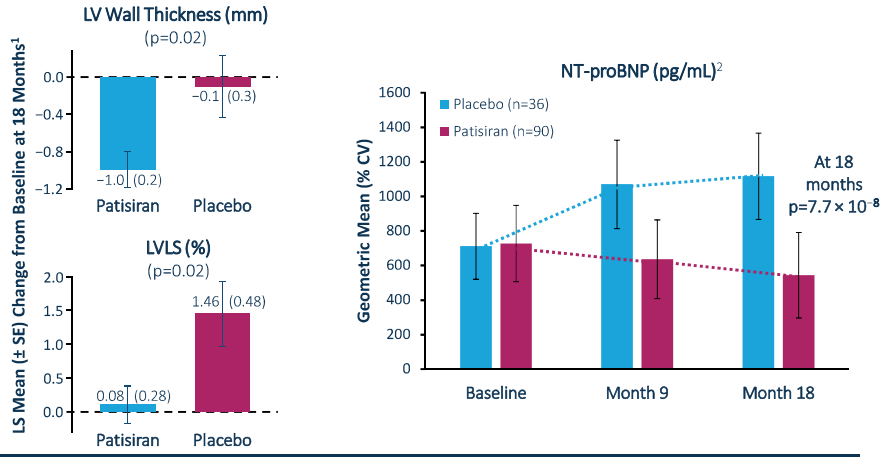
Patisiran Improved Measures of Cardiac Structure and Function Relative to Placebo in APOLLO Patients with Cardiac Involvement[a]



Patisiran improved measures of cardiac structure and function, and reduced NT-proBNP levels by 55% compared with placebo[1,2]

[a]Prespecified cardiac subpopulation: patients with baseline LV wall thickness ≥13 mm and no aortic valve disease or hypertension in medical history
CV, coefficient of variation; LVLS, left ventricular longitudinal strain
1. Adams et al. *N Engl J Med* 2018;379:11–21; 2.Solomon et al. *Circulation* 2019;139:431–3.

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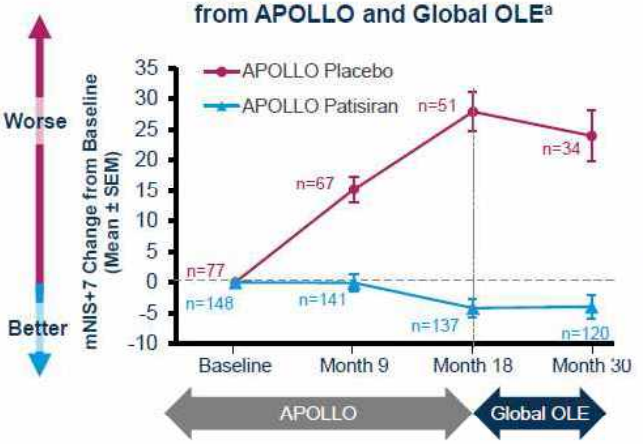
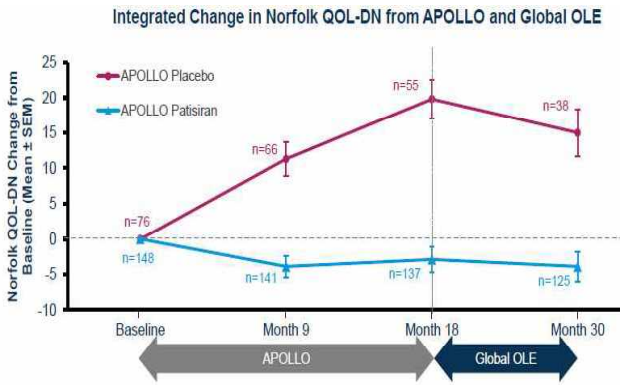
Long-term Safety and Efficacy of Patisiran in Patients with hATTR Amyloidosis: Global OLE Study

Michael Polydefkis[1], Alejandra González-Duarte[2], Teresa Coelho[3], Jonas Wixner[4], Arnt Kristen[5], Hartmut Schmidt[6], John L Berk[7], Quinn Dinh[8], Erhan Berber[8], Marianne Sweetser[8], Matthew T White[8], Jing Jing Wang[8], and David Adams[9]

Integrated Change in mNIS+7 from APOLLO and Global OLE[a]



Integrated Change in Norfolk QOL-DN from APOLLO and Global OLE



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PATISIRAN (RNAi)

INOTERSEN (ASO)

Table 2. Summary of Adverse Events.*

Event	Placebo (N=60)	Inotersen (N=112)
	no. of patients (%)	
Any adverse event	60 (100)	111 (99)
Event related to trial regimen†	23 (38)	87 (78)
Any serious adverse event	13 (22)	36 (32)
Event related to trial regimen†	1 (2)	8 (7)
Glomerulonephritis	0	3 (3)‡
Thrombocytopenia	0	2 (2)
Deep-vein thrombosis	1 (2)	1 (<1)
Intracranial hemorrhage	0	1 (<1)§
Tubulointerstitial nephritis	0	1 (<1)¶
Pulmonary embolism	0	1 (<1)
Embolic stroke	0	1 (<1)
Myelopathy	0	1 (<1)
Death	0	5 (4)

Table 3. Safety and Side Effects.

Event	Placebo (N=77)	Patisiran (N=148)
	no. of patients (%)	
Any adverse event	75 (97)	143 (97)
Adverse events occurring in ≥10% of patients in either group		
Diarrhea	29 (38)	55 (37)
Edema, peripheral	17 (22)	44 (30)
Fall	22 (29)	25 (17)
Nausea	16 (21)	22 (15)
Infusion-related reaction	7 (9)	28 (19)
Constipation	13 (17)	22 (15)
Urinary tract infection	14 (18)	19 (13)
Dizziness	11 (14)	19 (13)
Fatigue	8 (10)	18 (12)
Headache	9 (12)	16 (11)
Cough	9 (12)	15 (10)
Vomiting	8 (10)	15 (10)
Asthenia	9 (12)	14 (9)
Insomnia	7 (9)	15 (10)
Nasopharyngitis	6 (8)	15 (10)
Pain in extremity	8 (10)	10 (7)
Muscular weakness	11 (14)	5 (3)
Anemia	8 (10)	3 (2)
Syncope	8 (10)	3 (2)
Adverse event leading to discontinuation of the trial regimen	11 (14)	7 (5)
Adverse event leading to withdrawal from the trial	9 (12)	7 (5)
Death	6 (8)	7 (5)
Any serious adverse event	31 (40)	54 (36)
Any severe adverse event	28 (36)	42 (28)

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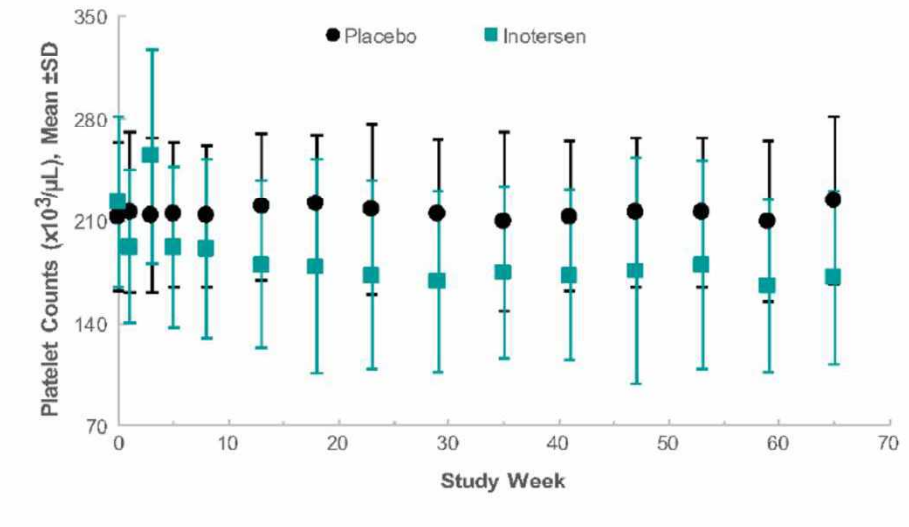
Figure S11. Mean Platelet Count Over Time*



* Data shown are from the protocol-specified clinic visits as defined in the original protocol.

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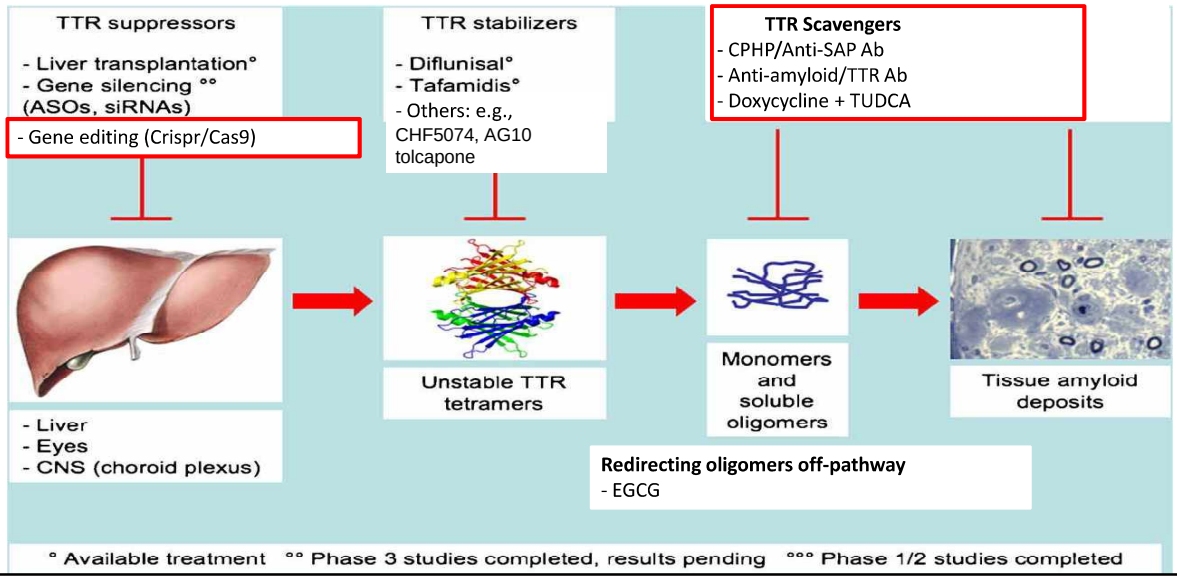
Therapeutical approaches for Transthyretin-related Amyloidosis

Modified from *Philippe Kerschen, MD[1]*
Violaine Planté-Bordeneuve, MD, PhD[2,3,]* Curr Treat Options Neurol (2016) 18: 53



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FAP Stage 1 — Tafamidis — CUP: - Patisiran - Inotersen

FAP Stage 2 — EAP/CUP: - Patisiran (Onpattro) - Inotersen (Tegsedi)

Clinical trials: Helios-A = s.c. siRNA
Trials to address cardiomyopathy

FAP Stage 3 — (Diflunisal)

Role for liver transplantation?

Brain and eye?

50

Much better scenario but novel problems

When to start treament? Definition of disease start (from presymptomatic to symptomatic, how to monitor presymptomatic subjects). Treatment in the presymptomatic phase?

Is there still a role for liver transplantation?

Tafamidis in early phases (20 mg/die; 80 mg/die?) / or siRNA-ASO?

Diflunisal in advanced stages

Combined treatments?

Address brain and eye

i.v. versus s.c – safety (new ASOs and siRNAs)

Gene silencing for cardiomyopathy (trials)

Economic sustainability

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P. Saveri
D. Calabrese
(A.Cortese)
E. Mauro
C. Pisciotta
E. Salsano

S. Magri
F. Taroni

Pavia
L. Obici
A. Lozza
(A. Cortese)
G. Merlini

Roma
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Overall Safety in the Global OLE

Patients with ≥1 Event, n (%)	APOLLO Placebo n=49	APOLLO Patisiran n=137	Phase 2 OLE Patisiran n=25	Global OLE Total n=211
AE	48 (98)	131 (96)	25 (100)	204 (97)
Severe AE	23 (47)	35 (26)	3 (12)	61 (29)
SAE	28 (57)	48 (35)	6 (24)	82 (39)
IRR	13 (27)	10 (7)	2 (8)	25 (12)
AE leading to study withdrawal	15 (31)	11 (8)	0	26 (12)
Death[a]	13 (27)	10 (7)	0	23 (11)

Integrated Exposure Adjusted Mortality Rates[b]

	APOLLO Placebo n=49	APOLLO Patisiran n=148	Phase 2 OLE Patisiran n=27	Global OLE Total n=224
Deaths[a], n (%)	13 (27)	15 (10)	2 (7)	30 (13)
Exposure-Adjusted Mortality Rate (CI), deaths per 100 patient-years	18.9 (10.4, 31.2)	3.4 (2.0, 5.4)	1.7 (0.3, 5.2)	4.8 (3.3, 6.7)

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