

„nothing is perfect“ –
Problems with triheptanoin
and clinical trials

MILAN, Italy, 7th – 8th October 2016



1st European
Conference
on GLUT1
Deficiency

Joerg Klepper



The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests.

The documents must be available at the Provider offices for at least 5 years.

Conflict of Interests Declaration

Undersigned **Prof. Dr. med. Joerg Klepper** as:

scientific responsible

moderator

teacher

speaker

tutor

of the event “**1st European Conference on Glut1 Deficiency**”

Milan - Italy, 7th-8th October 2016

Based on Art.. 3.3 about the Conflict of Interests, page 18,19 of the State-and-Region Agreement dated 19 April 2012,
managed by **Biomedica n. 148**

Declares

x that in the last two years HAD relationships about comercial financings with people having conflict of interests in the health field
(please specify the names):

Nutricia GmbH, Erlangen, Germany: travel costs and speaker honoraria

Vitaflo Pharma GmbH, Bad Homburg vor der Höhe, Germany: travel costs and speaker honoraria

*The State-and-Region Agreement asks for a declaration by Moderators, Speakers, Teachers and Tutors about the frankness of the financing sources and about their relationships with people with commercial interests within the last two years, only if there could be a conflict of interests.
The documents must be available at the Provider offices for at least 5 years.*

SLIDE N.2

Undersigned

First name Joerg Surname Klepper

Declares, under his responsibility, that in the report entitled

“Nothing is perfect – problems with Triheptanoin and clinical trials in Glut1DS”

There will be named the following Companies and / or Commercial Products:

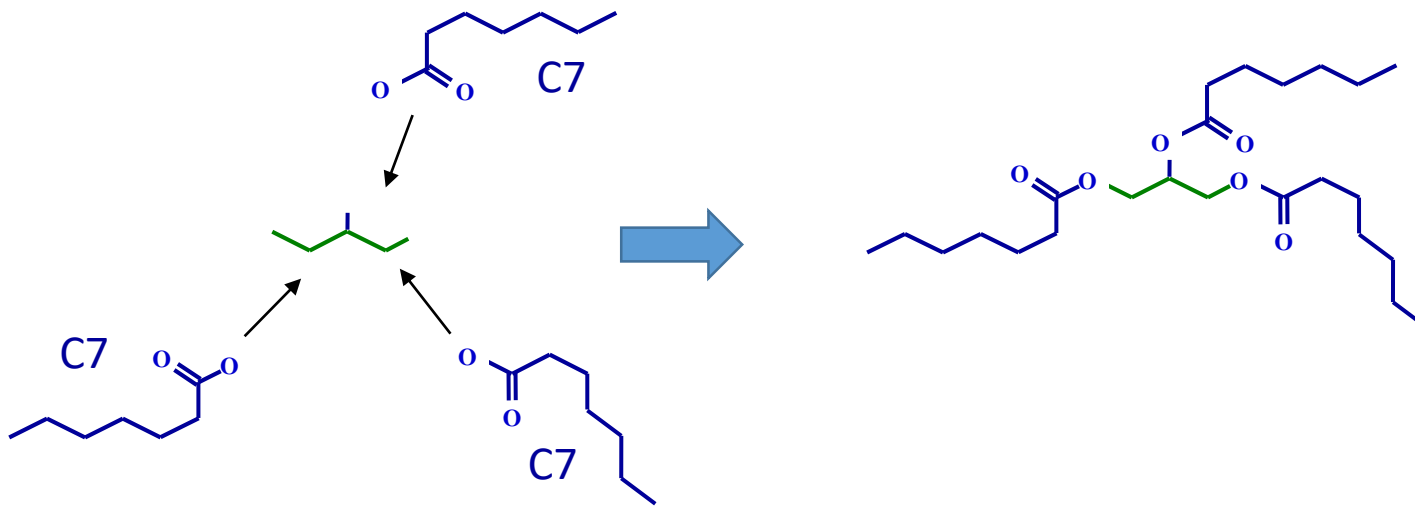
Ultragenyx Pharmaceutical Inc., Novato, USA

JUST WITH AN EDUCATIONAL AND SCIENTIFIC AIM OR TO REFER TO NATIONAL OR INTERNATIONAL GUIDELINES

Triheptanoin „C7“

Triheptanoin:

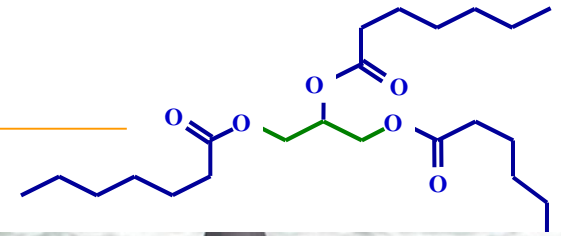
- C7-ketoester („artificial ketone“)
- used as tracer for butter in the EU
- liquid at RT with indifferent taste



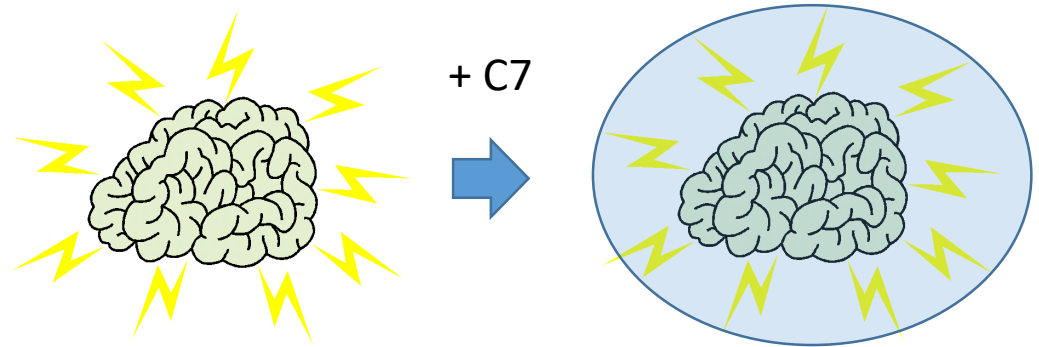
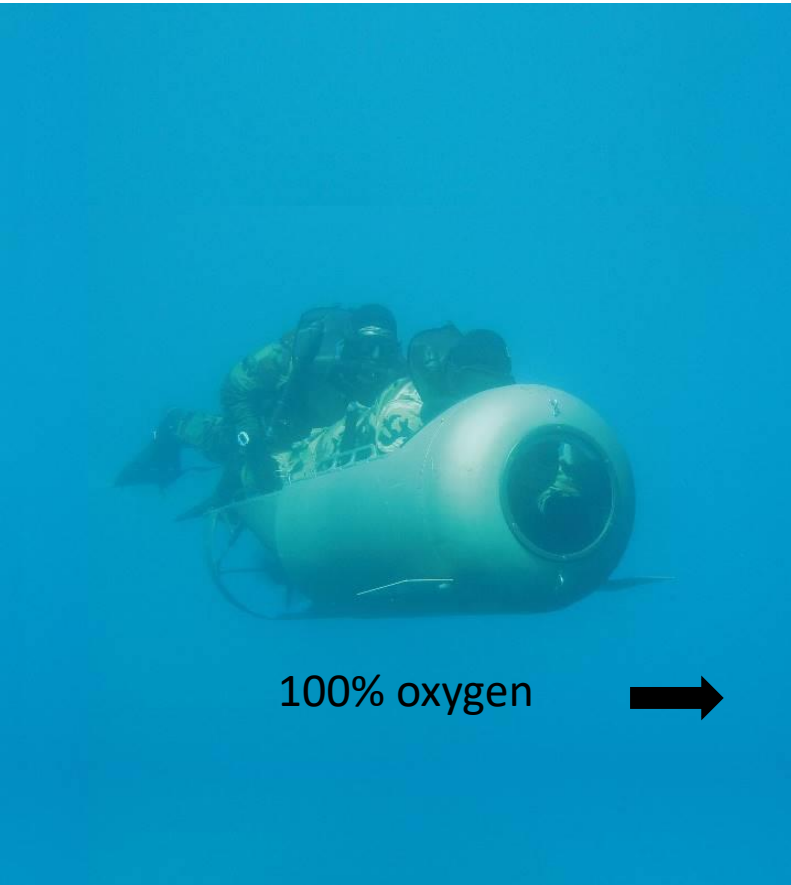
[Roe CR](#), [Brunengraber H](#)

Anaplerotic treatment of long-chain fat oxidation disorders with triheptanoin:
Review of 15 years Experience. [Mol Genet Metab.](#) 2015 Dec;116(4):260-8.

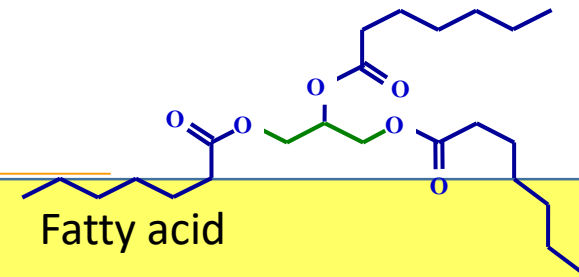
Triheptanoïn „C7“



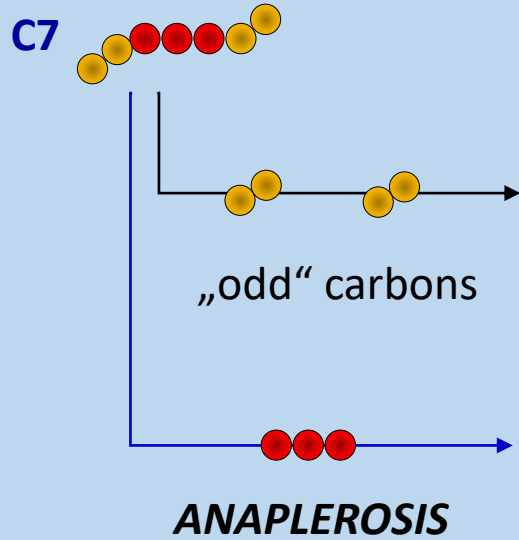
Triheptanoïn:



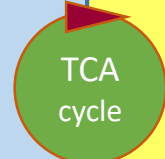
Triheptanoïn „C7“



triheptanoïn



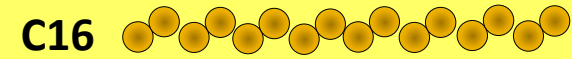
Acetyl-CoA



ATP

„plus...“

Fatty acid



„even“ carbons

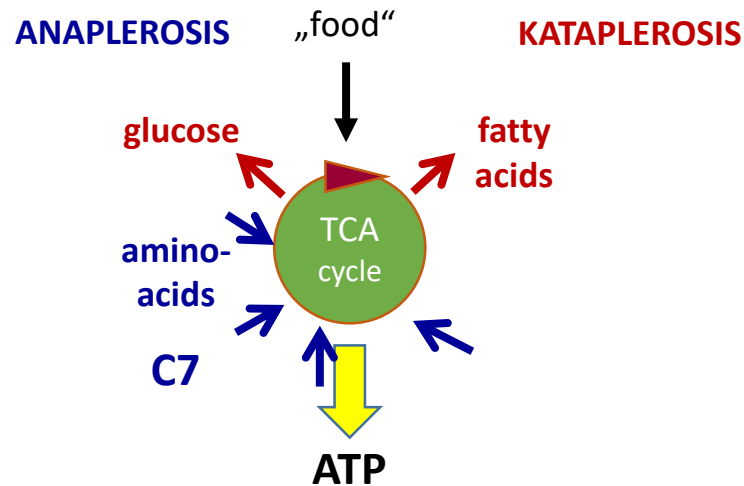
„ketone“

„Anaplerosis“

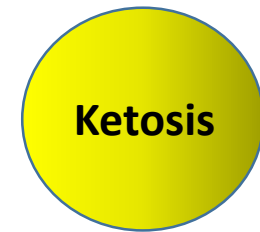
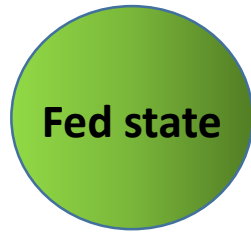
... a series of pathways that replenish the pools of metabolic intermediates in the TCA cycle.

If intermediates can be added to the TCA cycle, it is equally important to remove them.

„Kataplerosis“



„Anaplerosis“

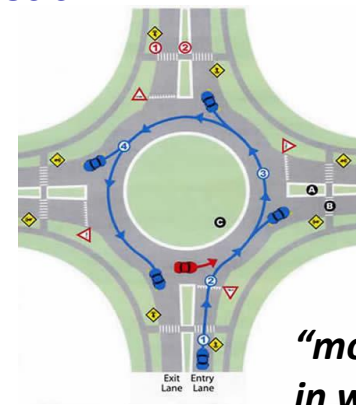


„Kataplerosis“

ANAPLEROSIS

„food“

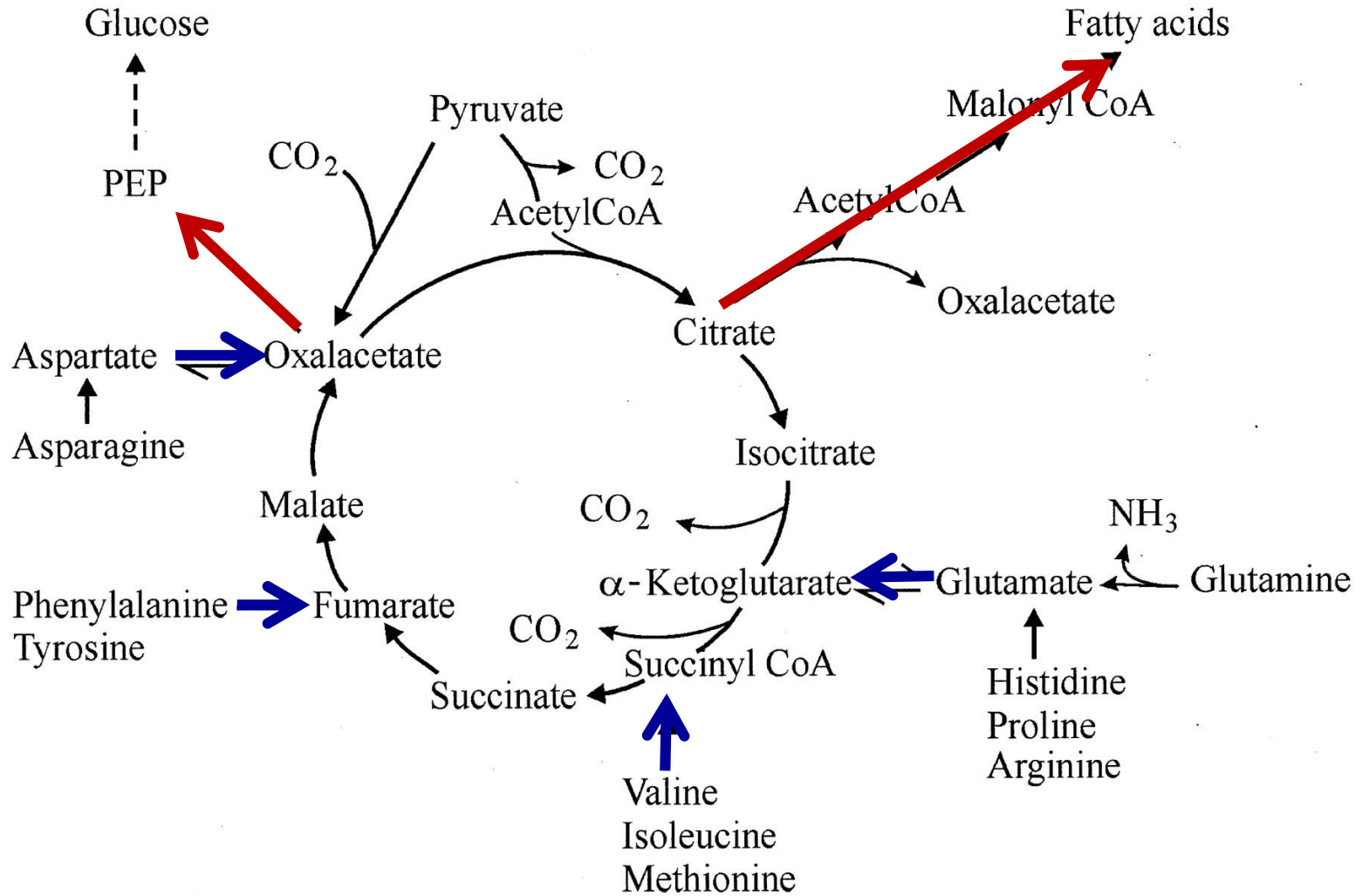
KATAPLEROSIS



ATP

“more like a traffic circle on a busy highway in which the flow of cars into the circle must be balanced by the flow out – or the entire traffic pattern will be interrupted with disastrous consequences.”

Anaplerosis and cataplerosis in the TCA cycle.

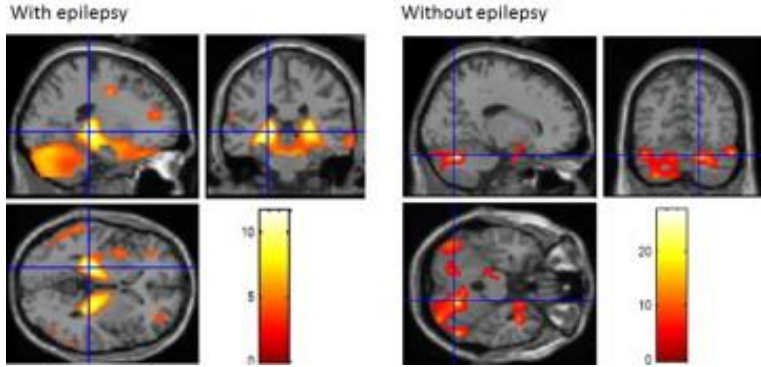


Oliver E. Owen et al. J. Biol. Chem. 2002;277:30409-30412

„how does triheptanoin work?“

¹⁸F FDG-PET

Glucose Hypometabolism in Glut1-DS

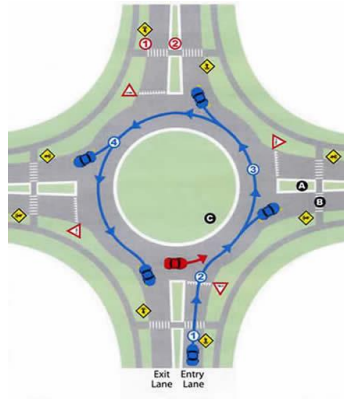


- thalamus
 - neocortical regions
 - cerebellum
- Movement control

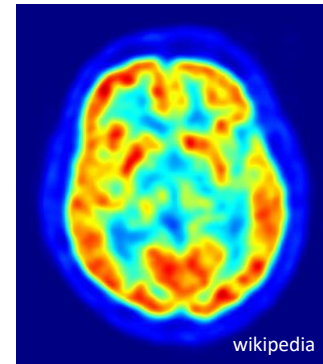
Akman CI et al
Epilepsy Res 2015

ANAPLEROSIS „food“

triheptanoin →



ATP



Pilot trial of Triheptanoin for GLUT1

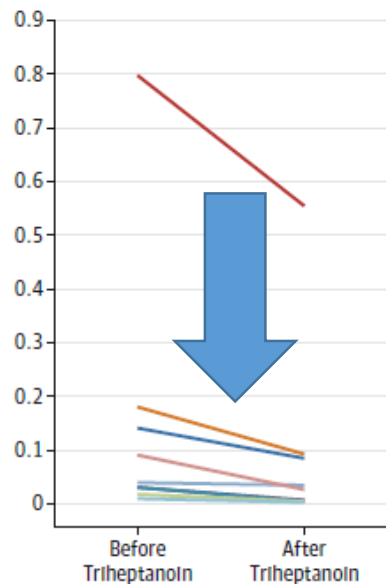
Original Investigation

Triheptanoin for Glucose Transporter Type I Deficiency (G1D) Modulation of Human Ictogenesis, Cerebral Metabolic Rate, and Cognitive Indices by a Food Supplement

JAMA Neurol 2014

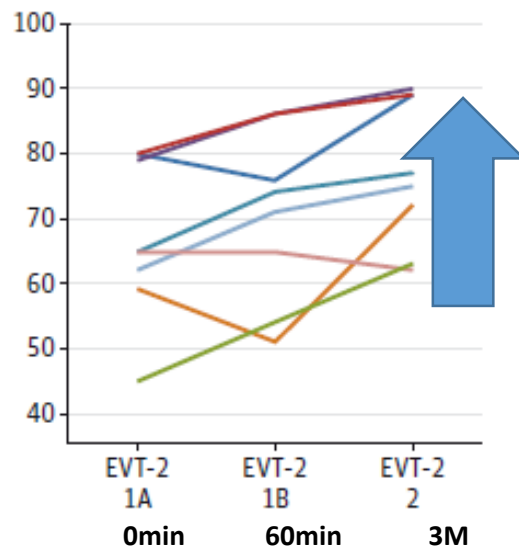


Seizure Rate:

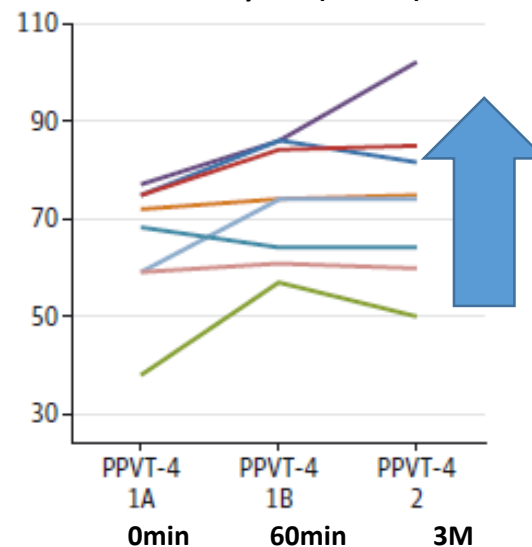


Neuropsychological scores

A Expressive vocabulary test (EVT-2)



B Standardized Peabody Picture vocabulary test (PPVT-4)



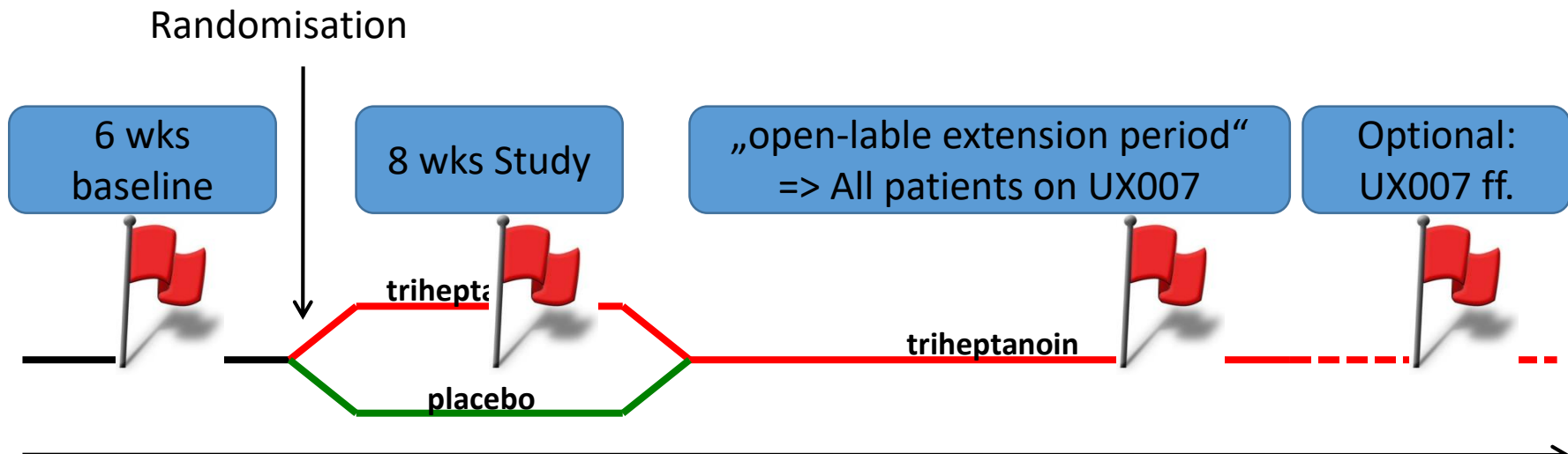
Conclusion:

- Triheptanoin can favorably influence neural function in G1D

Triheptanoin-Study UX007

Time period: Jan – Oct. 2014

Design: randomised, double-blind, placebo-controlled



52 Wks



-Triheptanoin as a) food supplement



b) drug (prescription)



- what happens with the data?

Triheptanoin-Study UX007

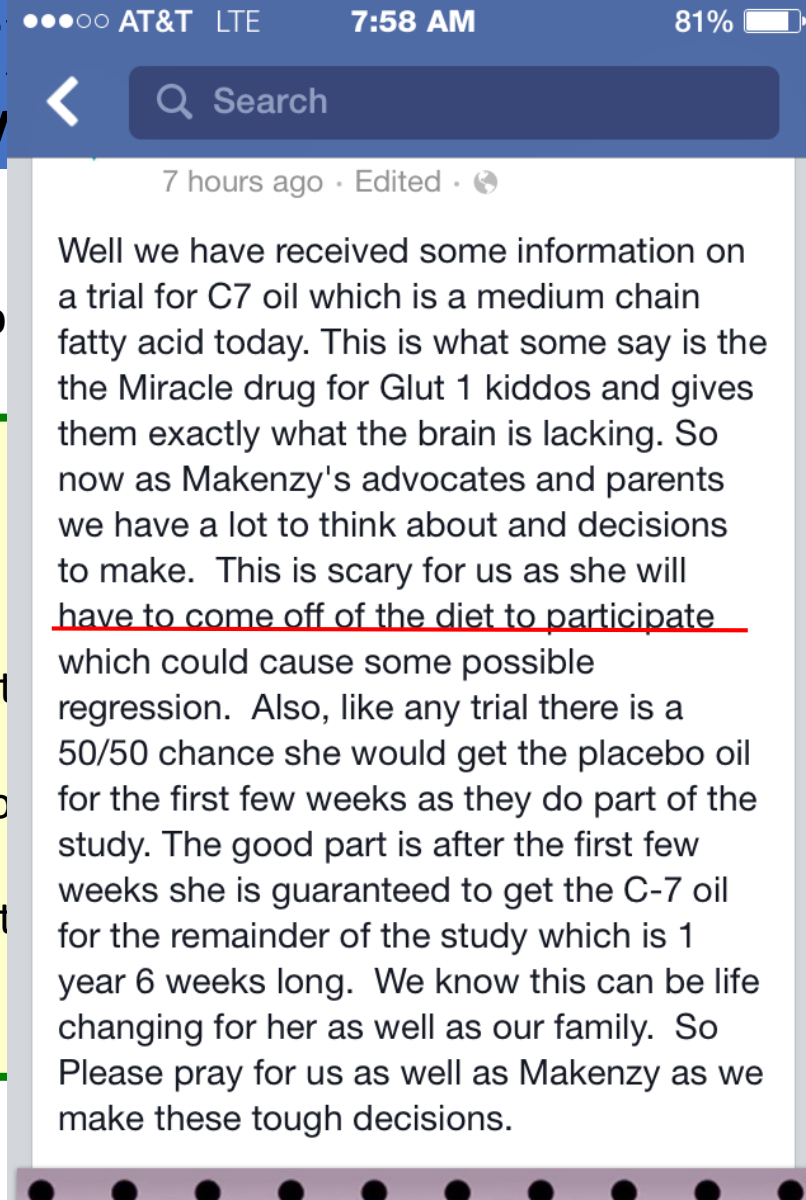
Phase 2 Study of Triheptanoin (UX007) Glucose Transporter Type 1 Deficiency

Time period: Jan – Oct. 2014

Design: randomised, double-blinded, placebo

Inclusion criteria:

- n=50, male + female., 3 – 17 yrs
- SLC2A1+
- at least 5 clinically manifest seizures within 6 months
- recurrent seizures despite 1 anticonvulsant
- Co-medication: 1-3 anticonvulsants (maintained for 6 months)
- no KD / uncompliant with KD prior/on study
- Beta-hydroxybutyrate ≤ 1 mmol/L (non-fasting stat)
- no trial with triheptanoin

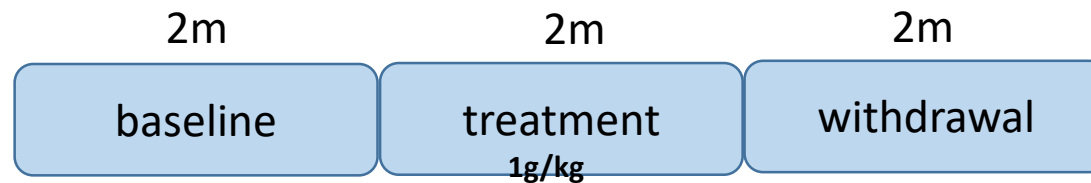


Triheptanoin-Study UX007

[Mochel F et al.](#) J Neurol Neurosurg Psychiatry. 2015 Nov 3

Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency.

Non-epileptic
paroxysmal
Glut1D
(n=8-2;7-47 yrs)



„Proof of concept“

**Paroxysmal
Events
(n = 6)**



<http://rghi.nl>

Triheptanoin-Study UX007

Phase 2 Study of Triheptanoin (UX007) for the Treatment of Glucose Transporter Type 1 Deficiency Syndrome (Glut1 DS)

Time period: Jan – Oct. 2014

Design: randomised, double-blinded, placebo-controlled

Hypothesis: better seizure control



Improves movement disorder

- n=50, male + female., 3 – 17 yrs
- SLC2A1+
- at least 5 clinically manifest seizures within 6 months prior to study / 4 at baseline
- recurrent seizures despite 1 anticonvulsant
- Co-medication: 1-3 anticonvulsants (maintained for study period)
- no KD / uncompliant with KD prior/on study
- Beta-hydroxybutyrate ≤ 1 mmol/L (non-fasting state!) at time of screening
- no trial with triheptanoin

DIETARY TREATMENT OF GLUCOSE TRANSPORTER TYPE 1 DEFICIENCY

Project Number: 1R01NS094257-01A1

UT SOUTHWESTERN MEDICAL CENTER

KDT 
C7 



Rationale:

- a) G1D is drug-refractory;
- b) no other G1D treatment is as versatile as partial dietary fat replacement with C7;
- c) the ketogenic diet is ineffective or intolerable for 1/3 of G1D patients;
- d) C7 impacts both neuropsychological performance and EEG spike-waves.

Aims in G1D patients receiving a normal diet:

1. determine C7 maximum tolerable dose and safety (primary outcomes)
2. evaluate the effect of partial C7 dietary replacement on
 - attention ratings (primary outcome)
 - EEG
 - neuropsychological / neurological performance indices;
3. explore C7 compatibility with KDT by evaluating
 - EEG
 - clinical seizures (primary outcomes)
 - ketosis and glycemia

Glut1D Databank

www.G1DRegistry.org

➔ Online-Questionnaire

Independent, accessible data bank

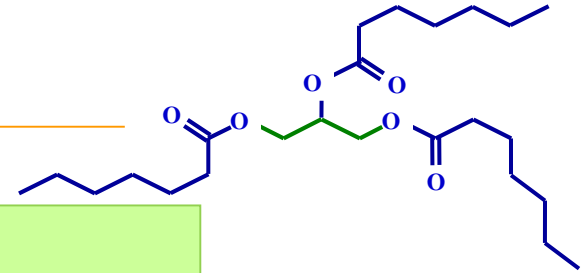


Prof. Pascual
Dallas, Texas

Unanswered questions:

- How many?
- Clinical classification („missing link“ between Glut1D type1+ type2...)
- Phenotype-genotype-relation
- Treatment response; Non-Responders?
- Long-term adverse effects; other tissues affected?
- What happens in puberty?
- Transition into adult neurology
- future therapies (trihexanoin)

Triheptanoin „C7“



PRO:

- artificial ketone
 - „effect“ via „anaplerosis“
 - safe, few side effects
- (experience in metabolic disease, mouse model, (human trial))

CON:

- high quantities needed
- long-term effects
- no replacement for KDT
- cost and availability?

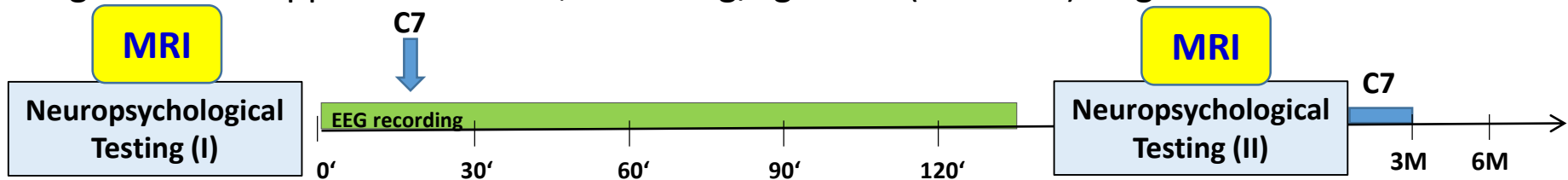
Triheptanoin for Glucose Transporter Type I Deficiency (G1D)

Modulation of Human Ictogenesis, Cerebral Metabolic Rate, and Cognitive Indices by a Food Supplement

Pascual JM et al.
JAMA Neurol. 2014 Aug 11
[Epub ahead of print]

Patients & Design:

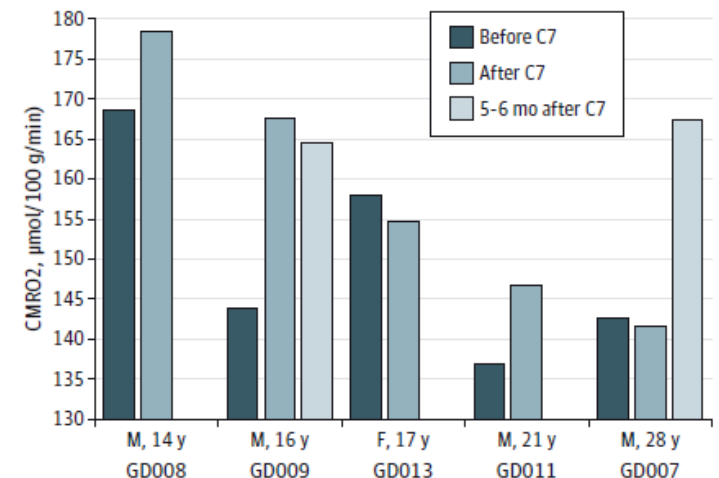
- 14 Glut1D patients (2-28 yrs) prior to KD treatment
- unsponsored, open-label case series
- regular food supplement with 0,75-1.0 mg/kg C7-oil (15-60 ml) single dose



Results:

- spike-waves ↓ by 70% (except in 1 patient)
- neuropsychological performance ↑
- cerebral metabolic rate ↑
- **adverse effects:**
 - none (n=11; 78%)
 - GI-Symptoms(n=03; 21%)
 - discontinued (n=01; 07%)

Figure 5. Magnetic Resonance Imaging-Measured Cerebral Metabolic Rate (CMRO₂) in Patients Before and After Acute Triheptanoin Oil (C7) Consumption

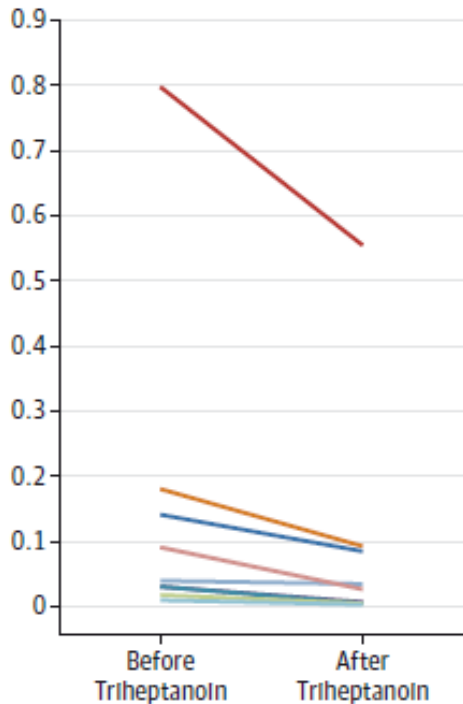


Triheptanoin for Glucose Transporter Type I Deficiency (G1D) Modulation of Human Ictogenesis, Cerebral Metabolic Rate, and Cognitive Indices by a Food Supplement

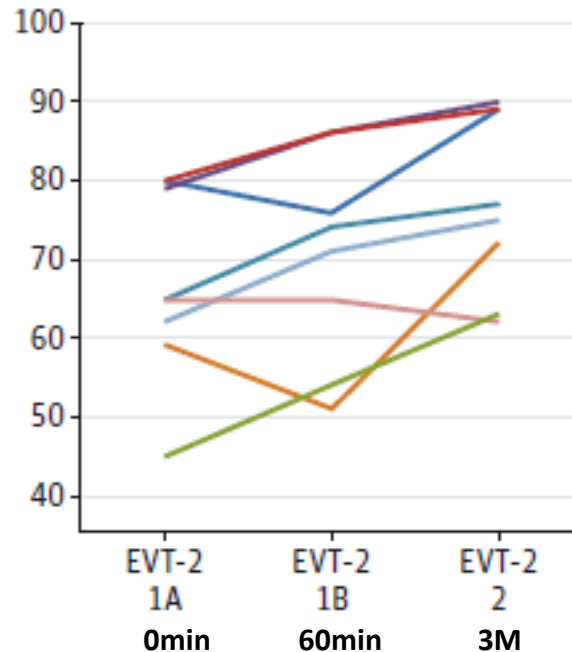
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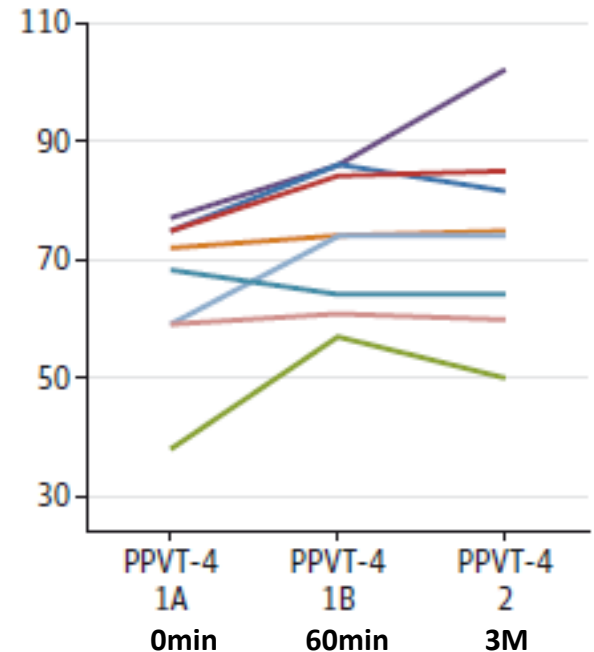
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Conclusion:

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