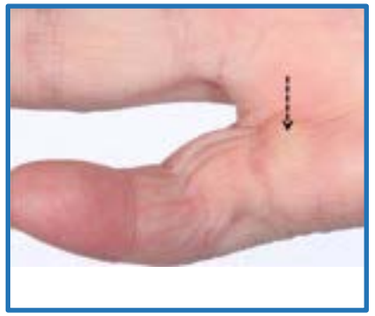
Initial Indication Targeting Dupuytren's Disease

- Common localized fibrotic condition of the hand, develops over years
- Nodules form under skin – eventually creating a thick cord pulling one or more fingers
- Can limit hand functions
- Unlike liver and lung fibrosis can be identified early

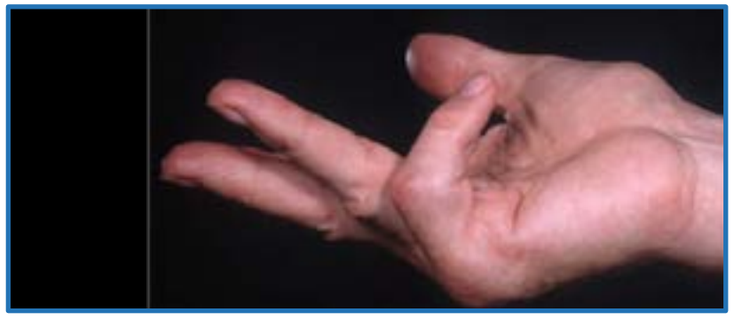
Early disease



No approved treatment: unmet need

Our trial is in early disease[1]

Late disease – results in impaired hand function



Current treatment options suboptimal: [2]

- Surgery – long (3 month) recovery, 6% recurrence at 5yr
- Needle perforation – less invasive, 30% recurrence at 5yr
- Collagenase injections – office procedure, 47% recurrence at 5yr

(1) Approval only from MHRA/CCMO and relevant accredited ethics committees.
(2) Layton T & Nanchahal J. F1000Research 2019, 8(F1000Faculty Rev): 231

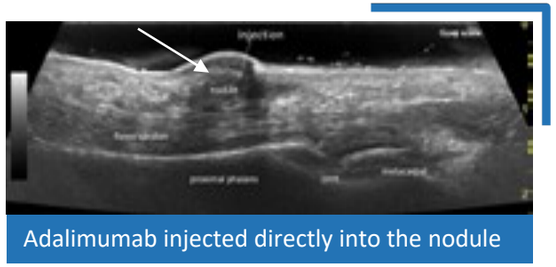
Phase 2a Completed: 40 mg (in 0.4ml) Adalimumab is Effective

The First Trial Of Any Targeted Therapy In Early DD[1]

EBioMedicine
Published by THE LANCET

: Anti-Tumour Necrosis Factor Therapy for Dupuytren's Disease: A Randomized Dose Response Proof of Concept Phase 2A Clinical Trial [2]

Trial Overview

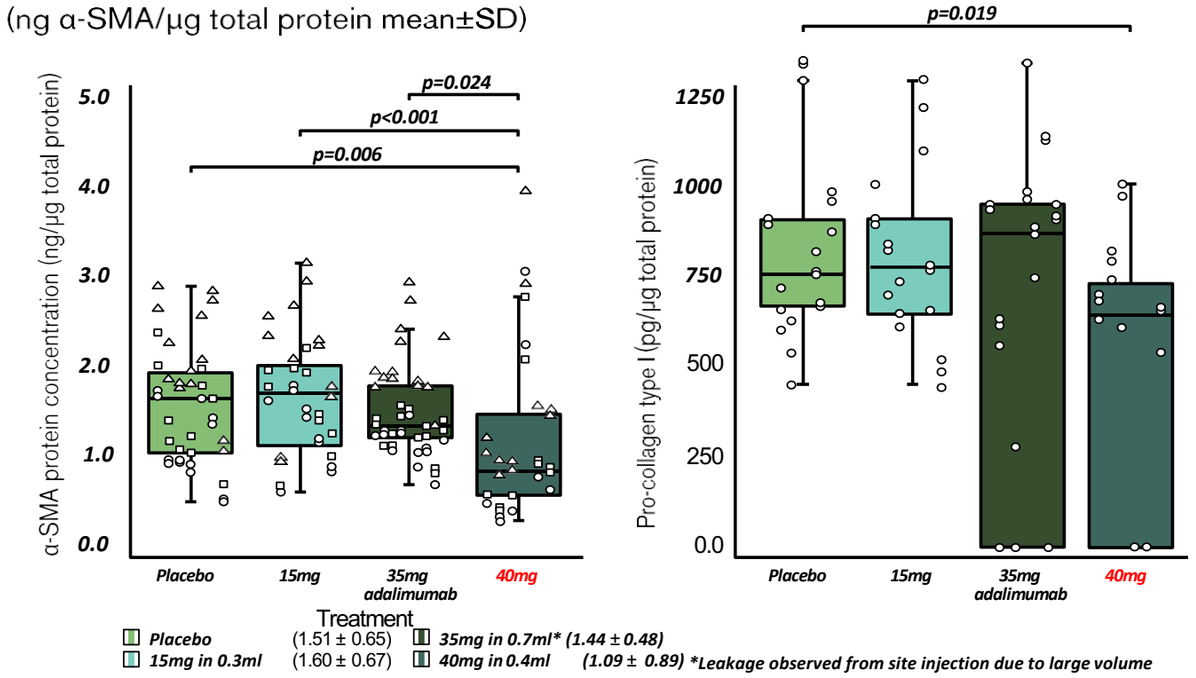


Adalimumab injected directly into the nodule

- Dose ranging with 28 patients.
- **40 mg in 0.4ml - effective dose.**
- Funded by HICF (Wellcome Trust + Dept of Health) and 180 Life Sciences

(1) Approval only from MHRA/CCMO and relevant accredited ethics committees.
(2) EBioMedicine 33 (2018) 282-288

Demonstrated efficacy at high concentration & dose



Phase 2b/3 Trial Fully Enrolled – Local Adalimumab in Early DD

- Randomized blinded trial in patients with early DD injected with optimal dose adalimumab(1)
- Every 3 months for 1 year (4 injections), following for a total of 18 months
- Outcome measures include nodule hardness, size and disease progression
- Randomized 181 patients across 3 sites in UK and the Netherlands

- **FULLY ENROLLED, FULLY PAID FOR**

- All UK patients have received final injection

- **Results expected Q4 2021**

- Trial sites: Oxford, Edinburgh, Groningen

	Objectives	Outcome measures
Primary Objective	To determine if injection with adalimumab is superior to placebo injection of normal saline in controlling disease progression.	Hardness of selected nodule.
Secondary Objectives	1. To compare the development of Dupuytren's nodules and associated cord, flexion deformities of the fingers and impairment of hand function for participants on each treatment.	1.1. Ultrasound imaging of nodule size. 1.2. Range of motion of the affected digit. 1.3. Grip strength. 1.4. Participant Reported Outcomes: Michigan Hand Outcomes Questionnaire (MHQ) Participant identified activity most restricted by DD scored on a scale of 1-10. 1.5. Clinical assessment of the hand.
	2. Monitor for adverse events.	2.1. Adverse event assessment comparing active and placebo groups using visual inspection of injection site and laboratory reports. 2.2. Progression to surgery of the digit being assessed.
Tertiary Objectives	3. To assess if early DD injection therapy represents good value for money compared to current clinical care. 4. Monitor circulating levels of adalimumab and antibodies to adalimumab in the blood.	3. Analysis of health care resource utilisation data and EQ-5D-5L data to estimate cost and utilities from participants on each treatment. 4. Analysis of blood sample.

(1) Approval only from MHRA/CCMO and relevant accredited ethics committees.

180 LIFE SCIENCES clinical trial 2b/3 - Nanchahal J et al, 2017 Wellcome Open Research, 2:37

Large Market Opportunity for Early Dupuytren's Disease

Estimated future worldwide market for Dupuytren's is a multi-billion dollar one [1]
All current treatments for Dupuytren's are for LATE stage disease

- 4% of the EU & US population suffer from Dupuytren's disease [1,2]
- Assume ~25% of these (1% total) are symptomatic & require treatment [3]
- Potential patients in the U.S. (1% of 315M) = 3M patients

- Conservatively assume 25% of symptomatic patients get treatment [4]

Geography	Population Assumptions	Number of Patients	Market Size *(assuming $1,000 treatment per patient)(5)*
USA	1% x 315M	~ 3.0M patients	$3.0B
EU	50% of USA	~ 1.5M patients	$1.5B

(1) Hindocha S, McGrouther DA, Bayat A (2009) Hand (NY) 4(3):256-69.
(2) Lanting et al. (2014) PRS 133: 593-603
(3) Nanchahal J, et al. (2017) Wellcome Open Res 2:37
(4) Layton T & Nanchahal J (2019) F1000Res Feb 28;8:F1000 Faculty Rev-231
(5) Based on current price of comparable anti-TNF treatments

Competitive Advantages

Developing the Only Treatment for Early Stage Fibrosis

- **Currently no competition for targeting and preventing early stage fibrosis**
- Non-surgical, easy to administer
- Short term treatment, intended to halt disease progression

Novel Use Of Human Disease Tissue To Identify New Targets In Fibrosis

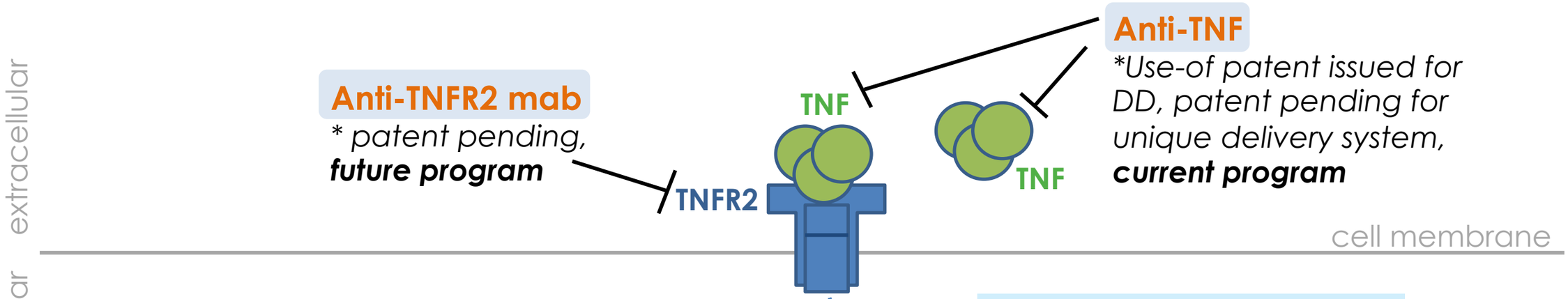
- Studies in DD lead the way for novel approach to develop clinical programs in other fibrotic diseases:
  - Tissues and cells from most fibrotic diseases not readily accessible as diagnosed late
  - Competitors use animals or late stage cells in culture, neither reflect human disease
  - **Our use of human tissue makes preclinical discovery more relevant and accurate, mitigating risk for clinical stage**

Cost Effective, Time Efficient, Academic Led Clinical Trials Performed in UK

- **Expert Investigators**
  - Established reputation in conducting clinical trials across academic and clinical networks (1)
  - Well practiced in publishing trials in peer reviewed clinical journals
- **Cost Effective**
  - No payment for trial patients required in the UK/EU
  - Staff costs can be covered by academic grants (Wellcome Trust, NIHR)
- **Shorter Timeline for Recruitment and Execution**
  - Access to large registries of patients/diseases
  - Regulatory expertise in writing protocols, seeking approvals, conducting trials.

(1) https://www.ndorms.ox.ac.uk/octru

Rationale for TNF Blockade in Fibrosis



180 LS drugs block TNF induced activation of pro-fibrotic pathways to reduce fibrosis

UNEXPECTED DISCOVERY – TNF/TNFR2 signaling activates Wnt pathway and transcription of fibrosis genes. Verjee…Nanchahal (2013)

PNAS

Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target

Liaquat S. Verjee [a], Jennifer S.N. Verhoekx [a,b], James K. K. Chan[a], Thomas Krausgruber [a], Vicky Nicolaidou[a], David Izadi [a], Dominique Davidson [c], Marc Feldmann [a, 1], Kim S. Midwood [a], and Jagdeep Nanchahal [a, 1]

[a] *Kennedy Institute of Rheumatology, University of Oxford, London W6 8LH, United Kingdom*
[b] *Department of Plastic and Rescontructive Surgery, Erasmus Medical Centre, 3015, Rotterdam, The Netherlands*
[c] *Department of Plastic Surgery, St John's Hospital, Livingston EH54 6PP, United Kingdom*

Wnt activation leading to FIBROSIS (↑ expression of a-SMA, Col1A1 genes etc)