Initial Indication Targeting Dupuytren's Disease

Characteristics

- 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

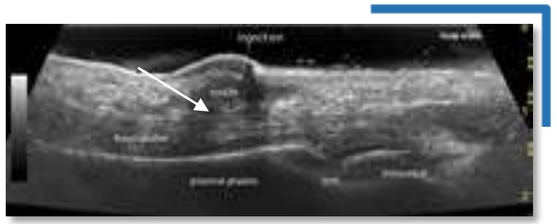
Phase 2a Completed: 40mg (in 0.4ml) Adalimumab is Effective

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]

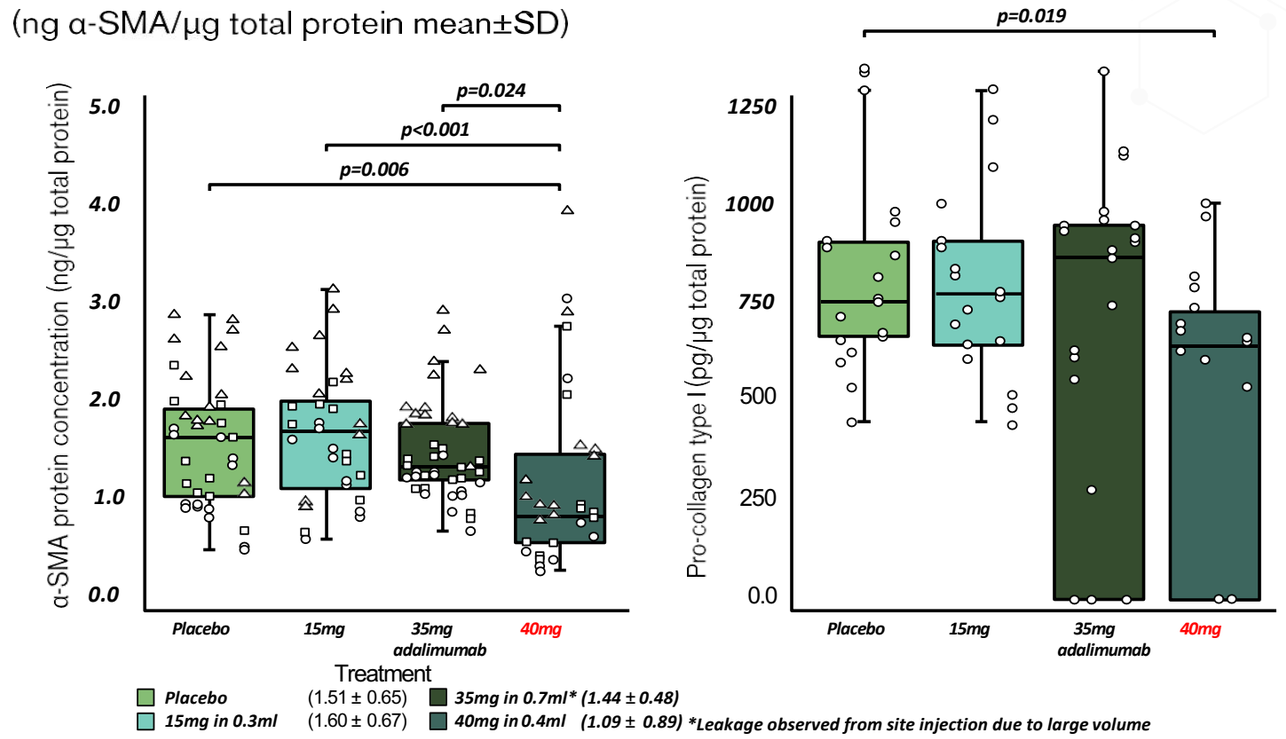
Trial Overview



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

Demonstrated Efficacy at High concentration & Dose



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

Phase 2b Trial: Local Adalimumab in Early Dupuytren's Disease

Description

- 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 the UK (Oxford, Edinburgh) and Netherlands (Groningen)

Funding

- Fully paid for by grants

Status

- Met both primary and secondary endpoints
- Almost all of the patients returned for all injections
- No related serious adverse events
- Manuscript submitted to a prestigious journal

	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.

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

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

Relatively High Prevalence of Dupuytren's Disease

~16M

US Prevalence

(5% of population; range 1-7%)

~12M	~3M	~800-900K
Fingers Not Sufficiently Bent to Need Treatment	Fingers Sufficiently Bent to Need Treatment	Severe Dupuytren's Treatment In-Effective
(75%; range 70-90%)	(19%; range 8-33%)	(5%)

Dr. Charles Eaton, Director of the Dupuytren's Foundation, provides the best prevalence estimates based on his regular assessment of the literature. Red Sky Partners reviewed his data with him.

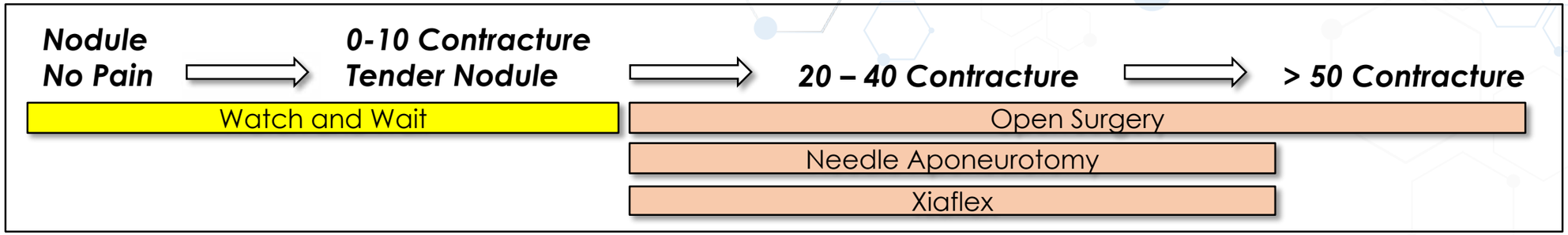
Many patients not seeking treatment and lack of a biological biomarker prevent accurate population estimates.

In a given year, the actual treated population is between 10% and 20% of the three million

Large Market Opportunity for Early Dupuytren's Disease

Estimated future market: >$1B worldwide[1]
All current treatments (surgery, Xiaflex): for LATE-stage disease only

Current Treatment Paradigms



Initial Launch and Label — **$300M-350M in US[2]**

1. **Soften cord/nodule**

Market Expansion Opportunities — **$500-800M in US[2]**

2. Tender Nodule | 1. Soften cord/nodule

2. Tender Nodule | 1. Soften cord/nodule | **3. Surgical Adjuvant**

5. Prevention | 2. Tender Nodule | 1. Soften cord/nodule | 3. Surgical Adjuvant | **4. Severe "Untreatable"**

(1) Hindocha S, McGrouther DA, Bayat A (2009) Hand (NY) 4(3):256-69.
(2) Estimate by Red Sky Partners, 2021

Large Market Opportunity for Early Dupuytren's Disease *cont'd*

Estimated future market: >$1B worldwide(1)
All current treatments (surgery, Xiaflex): for LATE-stage disease only

Initial Launch and Label: $300M to $350M (US only)(2)

Initial population target similar to Xiaflex but safer and non-invasive

- Proven effective at softening cord and nodule
- Does not preclude downstream options
- Aggressive social media patient outreach
- Physician education on mechanism
- Priced comparable to Xiaflex for treatment course
- Acceptable reimbursement plan to facilitate surgeon adoption

Market Expansion: $500M to $800M (US only)(2)

Further expand treated population and established efficacy drives share gains

- Safety and non-invasive profile drives earlier trial
- Patient outcomes and QOL improvements are positive
- Physicians have a new, safe option to offer patients seeking treatment and prevention of progression
- More, early patients seek and request treatment
- Improved cost benefit relative to Xiaflex and needle aponeurotomy
- Possibly expand to use by rheumatologists

(1) Hindocha S, McGrouther DA, Bayat A (2009) Hand (NY) 4(3):256-69.
(2) Estimate by Red Sky Partners, 2021

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

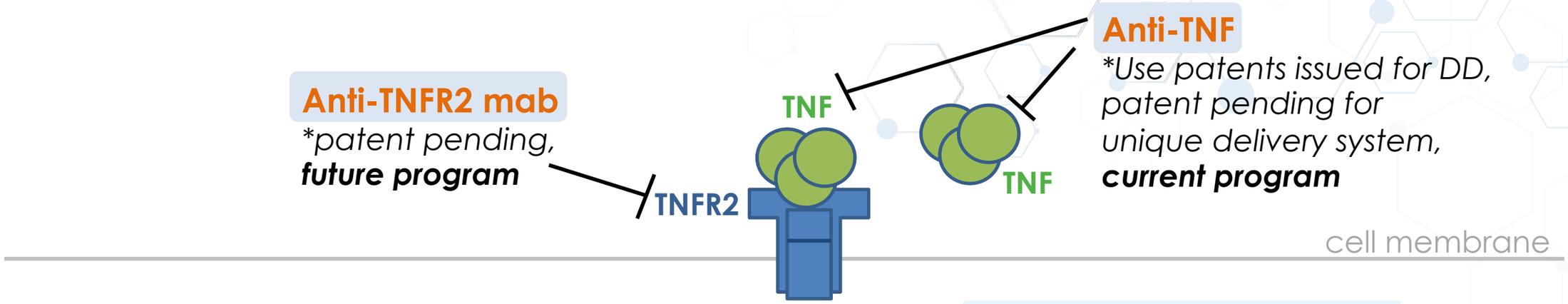
- Studies in DD lead the way for novel approach to develop clinical programs in other fibrotic diseases:
  - Tissues and cells from most fibrotic diseases not readily accessible as diagnosed late
  - Competitors use animals or late-stage cells in culture, neither reflect human disease
  - **Our use of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

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

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

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[b] Department of Plastic and Reconstructive 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)