Challenges of Early Phase Studies in Patients

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Introduction

- Operational Specialist

Shandon CLINIC GROUP

Lundbeck

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Improving quality of life

Scope

- Changing landscape of Phase 1
- Protocol
- Ethics and Regulatory
- Recruitment
- In-house
- Case study – Migraine model
- MAC study portfolio

Changing Landscape of Phase 1

- 20 years ago – all healthy volunteers
- Special populations
    - Smokers
    - Elderly
    - Post-menopausal
    - Asthma
    - Diabetic
- Last 10 years patient Phase 1 studies more common, patient cohort added to Phase 1 studies or studies conducted in entirely patients
    - Pressure for go, no-go decisions faster, smaller biotech companies want results fast to sell assets
    - More complex drugs
- Phase 1-4 used to be very stringent, now fuzzy lines
- Single site healthy volunteer study → multi-centre patient study
- Need in-house patient studies, NHS sites don't have the beds to perform quickly
- Phase 1 units struggle with patients!

Protocol challenges

- Integrated protocols
  - SAD, MAD, efficacy all under one banner
  - Need adaptive changes and flexibility to ensure no need for amendments
- Inclusion/Exclusion criteria
  - Due to nature of Phase 1 (safety and tolerability) and stage in development need patients with few other co-morbidities and concomitant medications
  - Osteoarthiritis studies, bi-lateral in knee KL 2-4, low BMI, no other co-morbidities or concomitant medications – average patient 60 or above
- SAD/MAD studies
  - Multi-centre, cohort design – much longer and require more money and co-ordination

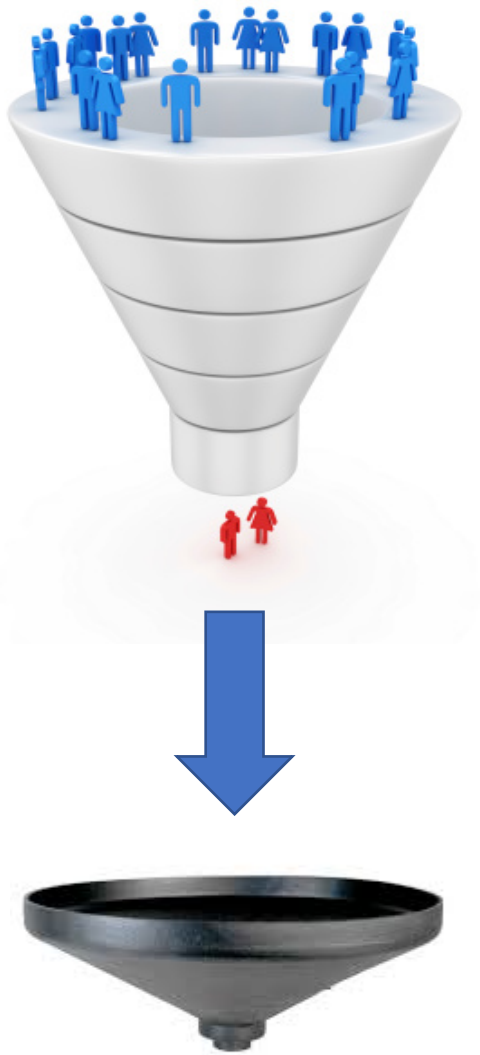
Ethics and Regulatory Challenges

- Ethics
  - Patients on Phase 1 studies single dose may have no benefits or placebo, may get exposure to IMP such as MAb which means they are restricted when they can take part again
  - But increased concerns using HVs in studies after TeGenero and Bial

- Regulatory
  - Standards in UK for Phase 1 studies in HVs especially FIM but not for patients (NHS sites can run FIM patient studies without following guidelines)
    - Phase 1 accreditation scheme (multi-centre across countries)
    - TOPs (not used NHS)
    - ID and photographs
  - UK environment special processes for Phase 1 standard HV studies e.g. faster regulatory and ethics, but need to tailor study in patients to be Phase 1 not 2a to use this

Recruitment challenges

- Stringent criteria make harder population to find, extending timelines of recruitment
- Need to make studies attractive to patients when little or no benefits
- HV speciality easy, one group people, patients much harder 1000s of different types how do you have experience of all?
- Patients with time commitments for stays in unit generally elderly – renal function
- Recruitment funnel almost flat



Operational challenges

- Depending on therapeutic area, specialist physicians needed, or support staff and possibly specialist care, equipment
- Timelines – not as efficient to run as HV studies, have to run patients as and when find them
- In-patient stays
    - Availability around work/family etc
    - Does unit meet expectations? Not a 5-star hotel
    - Entertainment of older age group
- May need repeated follow-up to return to normal

Operational challenges (part 2)

- Concomitant medications
    - Robust system in place for housing and dispensing concomitant medications
    - Number of studies where clients insisted patients should keep their own medications, patients tried to swap medications
- Placebo effect
    - Staff used to HV's and professional will react to patients differently (grandparent syndrome)
    - Patients get chance to chat to others with same condition, learn new things and swap ideas

So why do we do them?

- Interesting
- Chance to develop programs to get efficacy data much quicker
- MAC chooses to run all patient studies according to Phase 1 accreditation
- Designated as Early Phase unit, not Phase 1 unit
- Since opening June 2016 80% of studies have either had patient cohort or been all patients
    - FIM study, 1 cohort in-house HV safety/tolerability, 1 cohort patients in-house safety/tolerability, 1 larger cohort out-patient patients – company got data in 9 months which enabled sale of asset
    - Chronic diaorrhea (novel area) – rescue site, asked to find 15 patients, ended up completing 23

Migraine model – case study

- Healthy volunteer trials will provide information on safety, PK and tolerability but no information on patient dose
- Trials in patients are long and time consuming, particularly if no idea of dose
- Difficulty in showing efficacy of treatment if need to wait for a ‘natural’ migraine to occur in patients (e.g. get migraine at home, ring clinic, need to travel in etc)
- Models of migraine under report key data such as test-retest reliability.
- MAC formally assess a model of inducing migraine under test conditions which has been widely used academically

Study Design

- Patients
  - 20 Migraine patients recruited
  - Diagnosis confirmed by neurologist
  - Normally achieve pain relief by use of triptans

- Design
  - Four visits (3 Infusion; 1 placebo random order)
  - Immediate and delayed headache recorded for quality and intensity
  - Rescue medication (triptan) available 30 minutes after induction of delayed headache

Headline Results

Treatment	Presence of delayed headache			
	n = 0	n = 1	n = 2	n = 3
GTN	1	4	7	8
Placebo	11	9	NA	NA

GTN = glyceryl trinitrate; NA = not applicable. n: number of headaches experienced by one subject

Headline Results – Part 2

- Triptans administered 47 times
  - Delayed headache relief within 60 minutes in 43 cases
  - Delayed headache relief within 6 hours in all cases

- Delayed headache contained many of the features of a typical migraine
  - Unilateral
  - Pulsatile
  - Photophobia
  - Phonophobia
  - Nausea

Headline Results – Part 3

- Delayed headache morphologically similar to spontaneous migraine attack
- Not all subjects showed delayed headache – screening necessary in future studies?
- Induced headache treatable with known anti-migraine agents
- Infusion experience well-tolerated and no issues with repeat challenge
- 20 subject study completed in two months

Open floor discussion

- How can we change in UK to make better environment for Early Phase in Patients