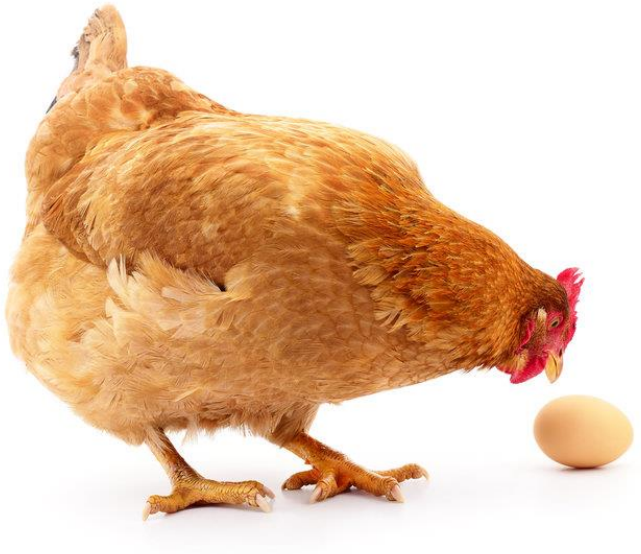
Regulatory considerations regarding the development of the SGS A/Belgium/4217/2015 H3N2 challenge agent



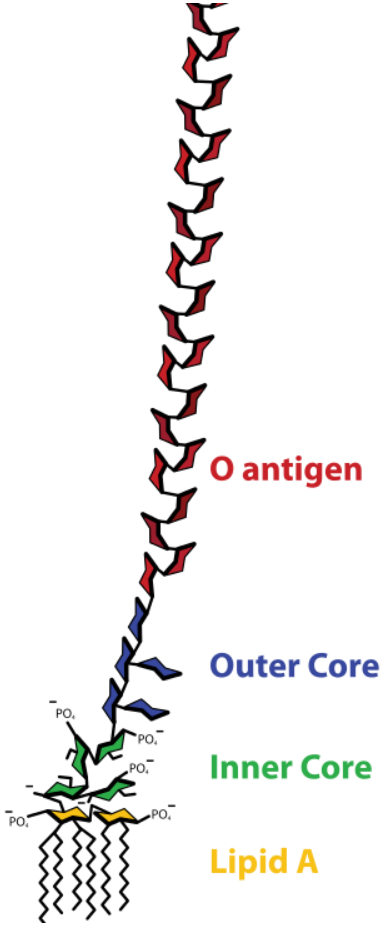
from chicken to challenge

Bruno Speder
Head Clinical Regulatory Affairs & Consultancy

WHEN YOU NEED TO BE SURE

SGS

SGS EXPERIENCE CHALLENGE TRIALS – PRIOR TO H3N2



- Human nasal lipopolysaccharide (LPS) challenge trials
- Viral challenge trials
  - H1N1 influenza challenge trials
  - Rhinovirus challenge trial

Viral Challenge Trials

Regulatory Requirements

CLINICAL PHARMACOLOGY UNIT (CPU / HCU)
ANTWERP, BELGIUM

HUMAN CHALLENGE UNIT – REGULATORY REQUIREMENTS

- Environmental permit
  - Biosafety Level 2 environmental permit
  - Subsequent use
- Biosafety requirements
  - 20 BSL2 compliant beds
  - Airlock / HEPA filtered negative-pressure system
  - Dedicated BSL2 lab
  - Standard Operating Procedures (SOPs)
  - Biosafety Committee consultation
- Biowaste disposal provisions
- Virus storage at Clinical Pharmacology Unit (CPU)

PERFORMING CHALLENGE TRIALS – REGULATORY REQUIREMENTS

- Pre-screening of volunteers
  - Update of pre-screening protocols with Ethics Committee
- Shedding of virus in community
  - Lenght of stay in unit: 11 days
  - Negative Biofire PCR before release of subject
- Influenza challenge trial during influenza season?
- Discussed in a Scientific Advice

H3N2 A/Belgium/4217/2015 H3N2
Development of a Challenge Agent

THE CASE FOR NEW CHALLENGE AGENTS

- Low vaccine efficacy has been evidenced for both matched and mismatched seasons (egg-adaptation; poor CoP)

- Challenge stocks currently in-use:
  - H1N1/2009pdm: both the ITS and NIH viruses show evidence of egg-adaptation
  - H3N2 A/Perth/16/2009: evidence of egg-adaptation; haemagglutinating, current strains are non-haemagglutinating

- Challenge studies are only as good as the challenge agent used

A/BELGIUM/4217/2015 H3N2 – DEVELOPMENT STRATEGY

- No guidelines for development of challenge agents
- Develop as Medicinal Product
  - Good Manufacturing Practice (GMP)
  - Non-clinical development
  - ‘First in Human’ phase I titration / characterisation trial
- Scientific Advice with Belgian Health Authority to validate development / manufacturing plan
- Challenge Agent Manufacturing Project (ChAMP)

MANUFACTURING APPROACH (1)

- H3N2 isolated from 14 year old at Stuivenberg Hospital
- Manufacturing approach
  - Based on vaccine guidelines
  - Combination EU and FDA guidelines
- Challenge agent manufactured as Solution for intranasal use
- Selection of contract manufacturer (CMO)
  - Meridian Life Sciences, Memphis; US
  - GMP classification audit

MANUFACTURING APPROACH (2)

- Adventitious Agent testing program established
- The nucleotide sequence A/Belgium/4217/2015 (H3N2) established (Next Gen Sequencing)
  - Waiving of neutralization assays till after phase I titration trial
- Release by Qualified Person (QP) before use
  - Update of GMP Manufacturing Licence
- CMC described in Investigational Medicinal Product Dossier (IMPD)

NON-CLINICAL DEVELOPMENT (1)

- In *vitro* characterisation assay
- In *vivo* characterisation study (GLP) in 30 ferrets
  - Group 1: intranasal administration with PBS (placebo, negative control)
  - Group 2: intranasal administration with Influenza virus H3N2 dose 1 (high dose)
  - Group 3: intranasal administration with Influenza virus H3N2 dose 2 (low dose)
  - Group 4: intratracheal administration 10^6 TCID50 of Influenza virus pH1N1 (positive control)
- *In vitro* and *in vivo* efficacy shown

NON-CLINICAL DEVELOPMENT (2)

- Pharmacokinetics and Product Metabolism in Animals
  - Not performed
- Toxicology
  - No formal toxicology studies performed, virus is not overtly virulent or pathogenic
- Reprotoxicology
  - Not performed: contraceptive precautions as CTG-3 anticonception guidelines
- Results described in Investigators Brochure (IB)

FIH TITRATION ChAMP TRIAL (1)

- ChAMP trial
  - *An Open-Label, Ascending Dose Study to Determine the Safety and Attack Rate of a Wild Type, Seasonal H3N2 Influenza Challenge Agent in Healthy Volunteers*
  - EudraCT Number: 2016-002737-29

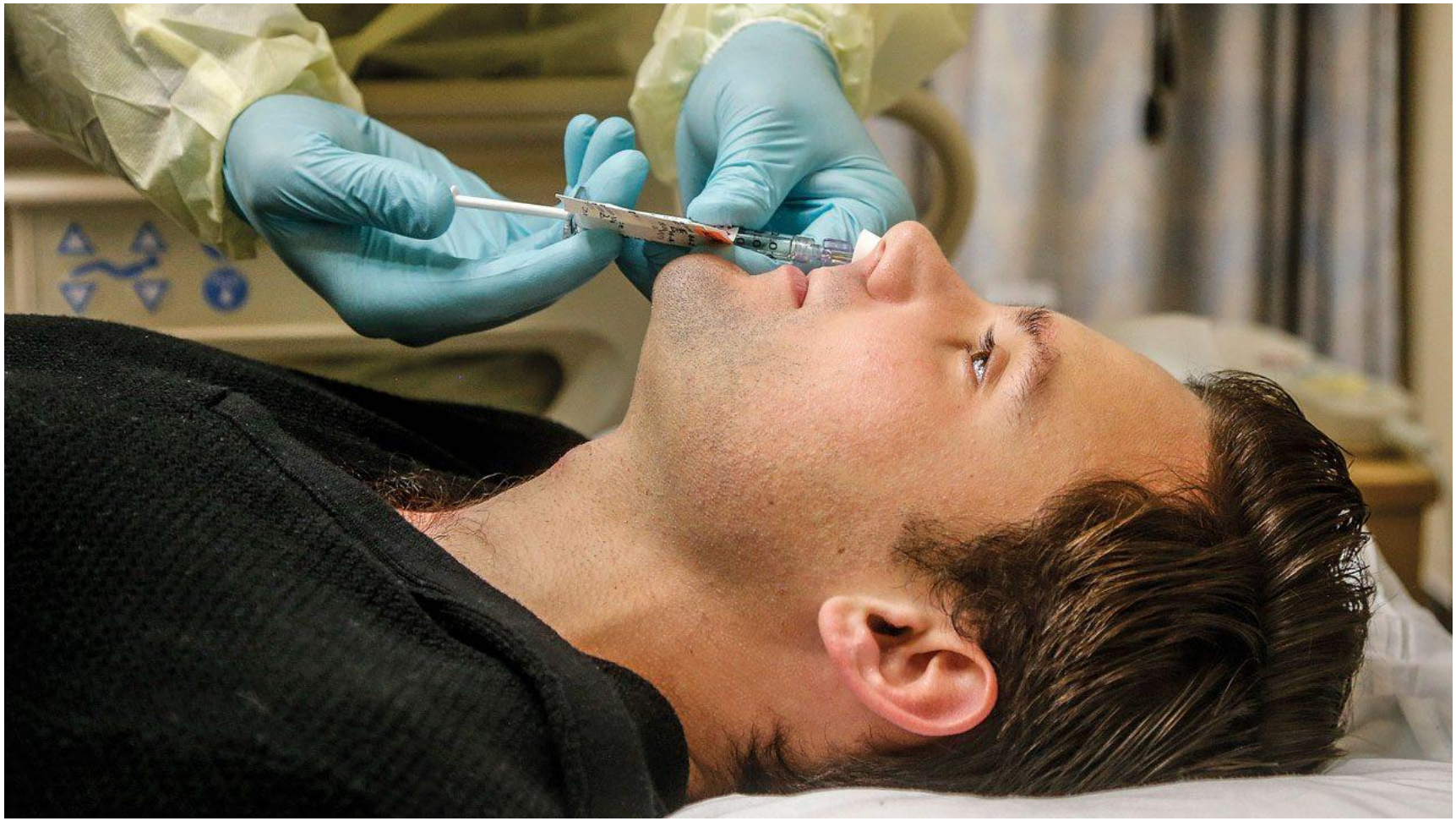
- Primary objectives:
  - The primary objective of the study was to determine the dose of live, wild-type H3N2 virus that had an acceptable safety profile and had an observed attack rate of >60% (i.e. at least 8 out of 12 subjects infected).

- Sponsor: SGS Life Science

FIH TITRATION ChAMP TRIAL (2)

- Is a titration trial a clinical trial according to EU directive 2001/20/ EC?
- Insurance requirements
  - Sponsor trial insurance
  - Product liability insurance
- Clinical Trial Application (CTA) to
  - Ethics Committee
  - Competent Authority - FAMHP
  - Notification to Biosafety Committee
- Performed at SGS Phase I unit, Antwerp, Belgium between November 2016 and March 2017

FIH TITRATION ChAMP TRIAL (3)



FIH TITRATION ChAMP TRIAL (4)

	Cohort 1 12 volunteers	Cohort 2 12 volunteers	Cohort 3 12 volunteers
Challenge virus titer (TCID50/mL)	1x10Exp5	1x10exp6	6.76x10exp6
Gender Male	58.3%	75%	58.3%
Age (Mean+/-SD)	43.3+/-5.3	40.8+/-7.7	48.7+/-5.6
Race (%White)	100%	91.7%	100%
BMI (Mean+/-SD)	25.6+/-2.3	25.3+/-3.2	25.5+/-3.1
Ex-smoker (%)	41.7%	25%	50%
MNT titer ≥10	3	4	3
MNT titer <10	9	8	9

A/BELGIUM/4217/2015 H3N2 - CHARACTERISTICS SUMMARY

- A/Belgium
  1. Is a representative, seasonal, circulating, community isolate (clade 3C.3b)
  2. H3N2 strains are strongly associated with enhanced symptoms and raised peaked viral load vs seasonal H1N1
  3. Requires minimal passages (P3, MDCK2E1) to achieve a high final titre (6.8×10^6)
  4. Shows no evidence of egg-adaptation
  5. A/Belgium infections may be susceptible to Oseltamivir
  6. Final product shows 100% homology to the original isolate
  7. Is non-haemagglutinating
  8. Is antigenically similar to current vaccine candidates
- Human Challenge Trials with strong candidates may reduce late phase failure rates

ONGOING REGULATORY ACTIVITY

- Regulatory maintenance
  - Investigational Medicinal Product Dossier CMC file
    - Ongoing stability results update
    - Neutralisation assay results
  - Investigators Brochure
    - Yearly update
    - Update after each trial
  - Development Safety Update Report (DSUR)
- H3N2 currently stored at 3 locations throughout Europe
- GMP audit by the Belgian HA on ChAMP trial

CHALLENGE TRIALS WITH H3N2 A/BELGIUM/4217/2015

- Challenge agent non-Investigational Medicinal Product (non – IMP)
  - H3N2 IMPD / IB added in CTA submission

- First antiviral / H3N2 challenge trial
  - EMA Scientific Advice
  - FAMHP Scientific Advice
  - First Subject Dosed in May 2017

QUESTIONS ?

THANK YOU FOR YOUR ATTENTION

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