



## MF59<sup>®</sup> ADJUVANTED INFLUENZA VACCINE



### INFLUENZA PREVENTION FOR VULNERABLE POPULATIONS

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Global Medical Affairs  
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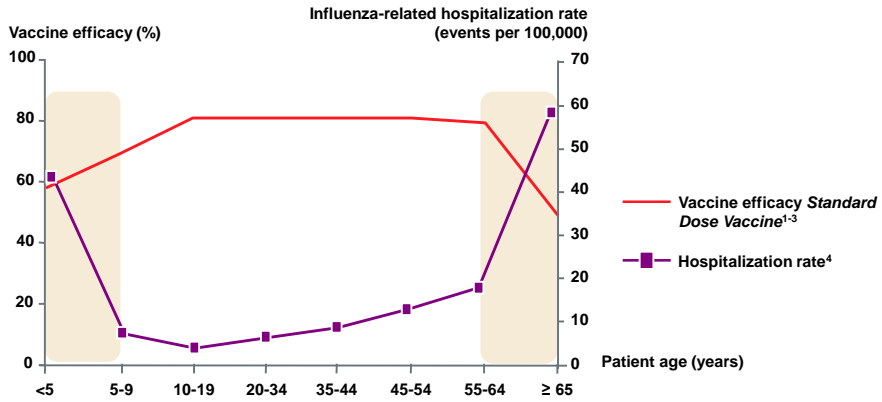
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## Objective

Provide an overview of the MF59<sup>®</sup> oil-in-water emulsion adjuvant, providing insights into the potential advantages of MF59<sup>®</sup> when combined with a flu vaccine



## Influenza Vaccine Efficacy is Lower While Related Complications are Highest at the Extremes of Age Improving Efficacy in the Young/Elderly is the Primary Need



Sources:

<sup>1</sup> Nichol K, et al. *Vaccine* 2003; 21:1769-1775

<sup>2</sup> Goodwin K, et al. *Vaccine* 2006; 24:1159-1169

<sup>3</sup> Grubeck-Loebenstein B, et al. *Nat Med* 1998; 4:870

<sup>4</sup> Glezen WP, et al. *Am Rev Respir Dis* 1987; 136:550-555

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## Adjuvants enhance the magnitude and breadth of the immune response

Individuals with a naive or weakened immune system respond less well to vaccines

Vaccines based on purified or recombinant antigens may induce a suboptimal immune response

Why enhance the immune response?

Vaccine antigen may not exactly match the circulating influenza virus strain

Vaccine antigen may be in short supply and access may be limited

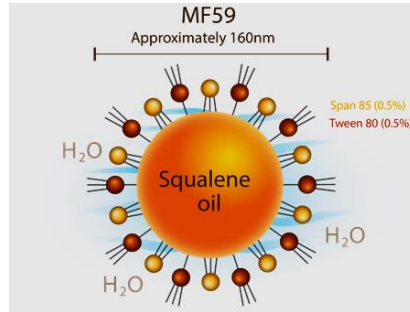
O'Hagan DT, et al. *Drug Discov Today*. 2009;14:541-551.



## Oil-in-Water Adjuvant: MF59®

### Composition

- First approved for use as an adjuvant in 1997, as part of FLUAD®
- MF59 is an oil-in-water emulsion composed of squalene, which is stabilized by Tween 80 and Span 85
- Squalene
  - **Biodegradable** and **biocompatible** oil
  - Intermediate precursor in the cholesterol biosynthetic pathway
  - Synthesized in the **liver** (>1g/day) and derived from **dietary sources** (50–200 mg/day)
  - Single dose of FLUAD® contains ~10 mg



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O'Hagan DT, et al. *Expert Rev Vaccines*. 2013;12:13-30.

**Seqirus**  
A CSL Company

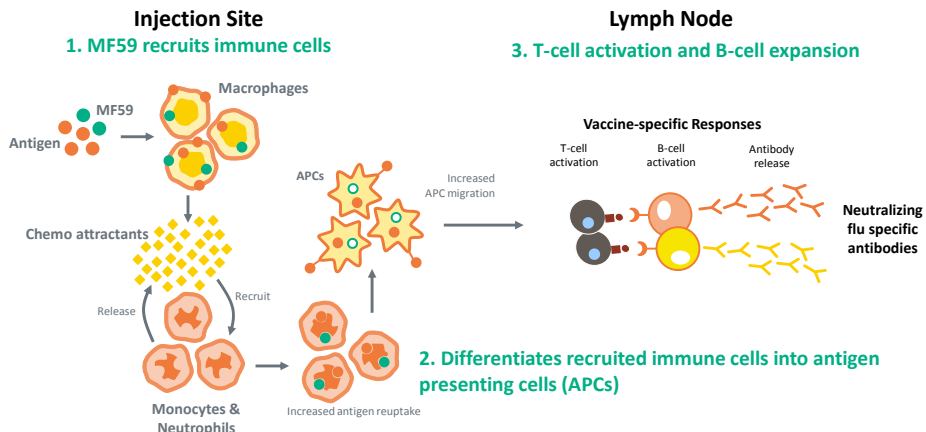
## Potential Benefits of MF59® Adjuvant in seasonal and pandemic influenza vaccines

FLUAD™ (Influenza Vaccine Adjuvanted)	MF59®	
<b>Improved outcomes</b>	<b>Antigen Sparing</b>	<b>Cross-reactivity</b>
Pediatrics - efficacy in RCT <sup>1,2</sup> Elderly – effectiveness studies <sup>3</sup>	Especially pandemic vaccine <sup>4</sup>	Improved breadth of immune response <sup>5</sup>
<b>Extensive Safety Data<sup>6</sup></b>		
<ul style="list-style-type: none"> <li>▪ Flud™ licensed in &gt;30 countries (1st approved Italy 1997)</li> <li>▪ &gt;100 million doses of MF59 adjuvanted vaccines distributed                             <ul style="list-style-type: none"> <li>▪ &gt;80 million seasonal Flud™ (elderly)</li> <li>▪ ~25 million H1N1 pandemic (incl pregnant women / young children)</li> </ul> </li> <li>▪ Data in ~120,000 subjects from clinical studies</li> </ul>		

1. Vesikari et al, *N Engl J Med*. 2011;365:1406-16.
2. Nolan et al. *Vaccine* 2014;32:6146–56
3. Iob et al, *Epidemiol Infect*. 2005;133:687–693; Mannino et al, *Am J Epidemiol*. 2012;176:527–53; Van Buynnder et al, *Vaccine* 2013;31:6122-8.
4. Novartis Vaccines data on file. Data from V111\_03; presented at ESPIID 2011
5. Ansaldi et al *Vaccine* 28: 4123-4129, 2010.
6. Novartis Adjuvant Trivalent Influenza Virus Vaccine (aTIV) [PDF document]. Retrieved from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM463633.pdf>

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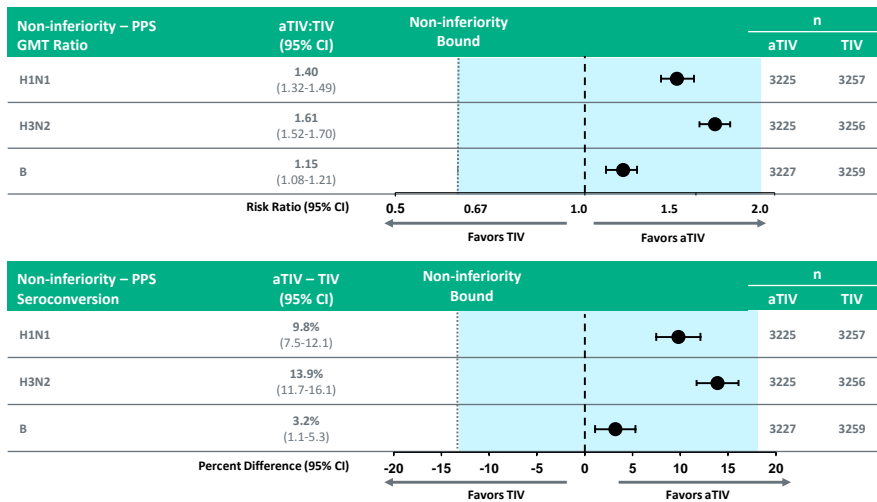
## Proposed MF59 Mode of Action at Injection Site



Seubert et al., J Immunol, 2008; Schultze et al., Vaccine, 2008.  
 Khurana et al., Sci Transl Med, 2010.  
 Calabro et al., Vaccine, 2011.  
 Vono et al., Proc Natl Acad Sci USA, 2013.



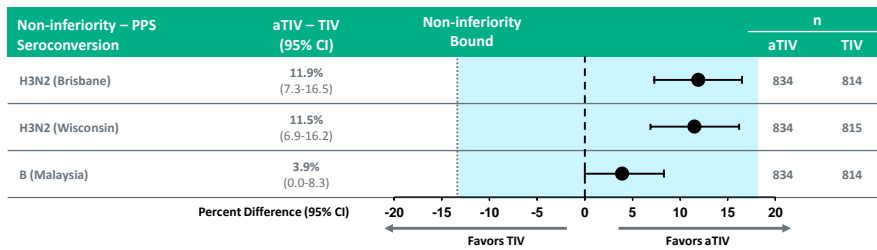
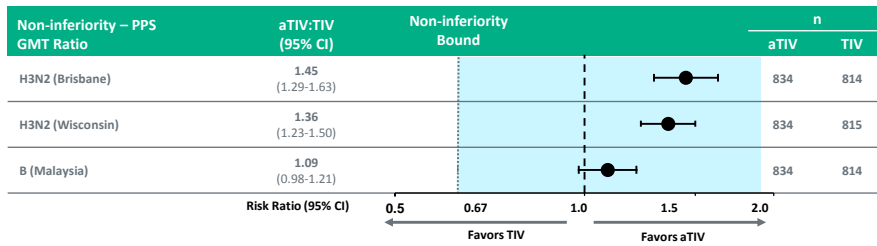
## Homologous Strains - Greater Differences in SC and GMT with aTIV



8 Novartis Adjuvant Trivalent Influenza Virus Vaccine (aTIV) [PDF document]. Retrieved from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM463633.pdf>



## Heterologous Strains - Greater Differences in GMT and SC with aTIV



Novartis Adjuvant Trivalent Influenza Virus Vaccine (aTIV) [PDF document]. Retrieved from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM463633.pdf>

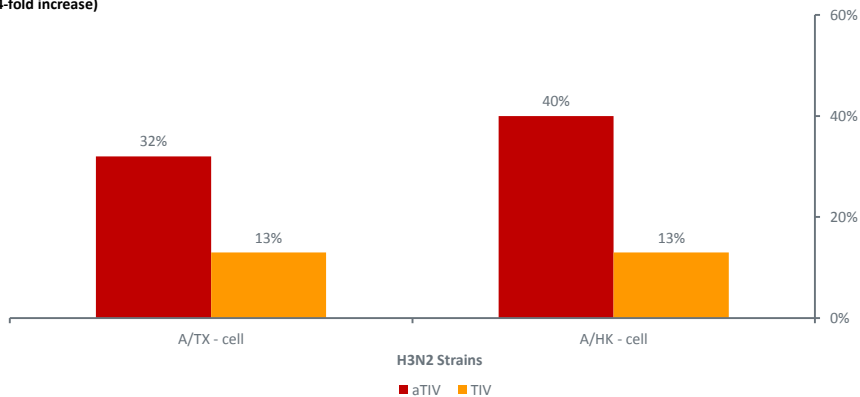
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## aTIV Expands Serologic Coverage of 14/15 NH H3N2 Mismatch

Adjuvanted vaccine generated a higher percentage of significant titer increase against both matched (A/Texas) and mismatched (A/Hong Kong) strains

Microneutralization Titers  
Seroconversion Rate  
(4-fold increase)



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Novartis Adjuvant Trivalent Influenza Virus Vaccine (aTIV) [PDF document]. Retrieved from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM463633.pdf>



## Effectiveness Study #1: Lombardia Influenza Vaccine Effectiveness (LIVE) Study

- Large community-based observational study
  - N=107,661 records, contributing 170,988 person-seasons of observation
  - Data derived through linked health administrative and hospital databases
- aTIV recipients at baseline:
  - More comorbidities
  - Higher functional impairment
  - More likely to be hospitalized
- aTIV recipients showed 25% risk reduction in hospitalization for influenza and pneumonia

Manino et al., Am J Epidemiol., 2012.

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## Effectiveness Study #2: Canadian Comparative Study

- Case-control test negative, community-based study in British Columbia
  - N= 282 available participants
  - PCR testing by BC CDC and linked to case-report forms from enrolled subjects
- aTIV recipients at baseline
  - More co-morbidities
  - More often over 85 years of age
  - More often resident in long-term care facilities,
- In older patients with co-morbidities, 63% vaccine effectiveness of aTIV vs. TIV in this H3N2-predominate season

Van Buynder et al., Vaccine, 2013.



## aTIV Overall Summary

- aTIV generated higher antibody titers
- aTIV well-tolerated, acceptable safety profile similar to other licensed vaccines
- aTIV demonstrated consistent enhanced effectiveness in LIVE and Canada Comparativeness study
- aTIV demonstrated higher immune responses to drifted strains in the 2014-2015 influenza season

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## 2016: Centenary Year for CSL



CSL 100 YEARS...

*JUST GETTING STARTED*

