CONTROLLING INFLAMMATION

Developing the First in Class Anti-C5a Antibody IFX-1: Lessons Learned from Clinical Trials

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The anti-inflammatory and tissue saving potential of IFX-1

Discussing the potential IFX-1 holds for various inflammatory disease indications
The Complement Pathways

The extrinsic pathway represents an additional route, outside of the well-known complement pathways, to activate C5.
The Terminal Complement Pathway

C5

C5 concentration in blood: ~75 µg/ml (~400 nM)

C5a concentration in blood: 10 ~ 30 ng/ml (~1-2.5 nM)

C5a

- strong amplifier of inflammation
- other ligands: C3a, ASP, C4a etc

C5aR

- cell activation
- cytokine generation

C5L2

- PKC-signalling
- HMGB-1 induction* (Inflammasome)

CSL2

- other signalling involved e.g. in triglyceride synthesis etc.

Membrane Attack Complex (MAC) triggers lysis of pathogens

C5b-9 = MAC

- C5L2 has a different binding pocket for C5a compared to other ligands like C3a, ASP etc. and this causes different cell signaling**. The C5a signaling has been shown to be pro-inflammatory*.

Inflammation

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Inflammation

* Rittirsch et al. Nat Med. 2008 May ; 14(5): 551; Colley et al. MABS. 2018,10 (1), 104
** Kalant D. et. al. J. Biol. Chem. 2003, 278 (13) 11123–11129
Songlin et. al. J. Biol. Chem. 2019; 294(21) 8384–839
The InflaRx anti-C5a Technology

C5

C5a

C5b

C5b-9 = MAC

MAC lysis
invading microorganisms

C5a conformational change

new epitope

IFX-1

KEY FEATURES

✓ Blocks C5a biological effects up to 100% in human blood
✓ Leaves MAC formation intact
✓ Binds with high affinity to the discovered epitope

Cleavage of C5 through:
• Complement pathway activation, or
• Directly through enzymes via “extrinsic” pathway
The C5a Blocking Potential of IFX-1 in Plasma of Patients suffering from Hidradenitis Suppurativa

5 nM IFX-1 highly effectively blocks HS-plasma / C5a-induced neutrophil activation in human blood

Data source: InflaRx GmbH in-house data
IFX-1 Specificity in Vitro and In Vivo

IFX-1 impact on Hemolytic Activity (CH50)*

IFX-1 impact on CH50 Analysis in Septic Patients**

**IFX-1 does not influence the hemolytic activity and leaves C5 cleavage and formation of C5b-9 (MAC) intact.**


** Data: InflaRx – Sepsis Clinical Trial Phase IIa
Neutrophil Activation Potential of C5a

Data Source: Prof. Peter Ward, University of Michigan

**C5a Mode of Action on Neutrophils:**
- chemotaxis of neutrophils (Shin et al 1968, *Science* 162,361-3)
- enzyme release (Goldstein et al 1974, *J. Immunol.* 113, 1583-8)
Potential of IFX-1 to Prevent Tissue Damage in H7N9 Induced Lung Inflammation

- IFX-1 treatment markedly improved the lung injury score in H7N9 infected lungs
- IFX-1 treatment strongly decreased viral load in H7N9 infected lungs

Sun et al., Clin Infect Diseases, 2014, Sept.
The tissue damaging effect of C5a
C5a as Key Player in Inflammation

**Strong Amplifier**
- Numerous publications
- Well understood MoA

**Neutrophils & Monocytes**
- Chemotaxis & Activation
- Adhesion
- O2 Radicals
- Enzyme release

**Macrophages**
- ROS production
- Release of granular enzymes

**Endothelials/vascular**
- Upregulation of C5aR
- ANGIogenesis
- Increased vascular permeability
- Adhesion molecules
- Coagulation, e.g. TF

**Blood**
- Coagulation increasing tissue factor

**proinflam. Cytokines**
- TNF-α, IL-1β, IL-6, IL-17
- Chemokines, e.g. IL-8
- HMGB-1
- others

**T-cells**
- Promote Th1/Th17
- Inhibition of Treg

**Epithelial cells**
- Upregulation of C5aR
- Tissue inflammation

> 5000 publications since the 1970th
Summary IFX anti-C5a Technology:

➢ Strong IP on discovered conformational epitope on C5a with protection until late in 2030 and with potential extension until late in 2035

➢ IFX-1 shows a superior performance:
  • up to 100% biological blocking activity towards its target C5a in a 1:1 ratio
  • leaves MAC formation intact – is highly selective

➢ IFX-1 has shown its anti-inflammatory potential in various settings

➢ IFX-1 and IFX-2 are based on the IFRX technology and are believed to be multi-applicable in various disease indications
Hearing clinical trials results and examining lessons learned
**Hidradenitis Suppurativa**

**CLINICAL FEATURES**
- Chronic, inflammatory, recurrent, debilitating skin disease of the hair follicles
- Most commonly in the armpit, groin and genital regions
- Extremely painful inflammatory nodules, boils or abscesses
- Draining fistulas leading to considerable scarring and functional disability
- Hurley staging system used to classify severity (stage I – III)

**PREVALENCE**
- Up to 200,000 moderate to severe (Hurley II+III) HS patients in US
- Higher prevalence in Europe with reports > 1% total HS prevalence

**CURRENT TREATMENT – MEDICAL NEED**
- Adalimumab (TNF-alpha inhibitor) from AbbVie is the only approved biological in US and Europe
- Accepted (but not approved) SOC includes topical, oral or i.v. antibiotics
- In some instances, surgery is required
- Approximately 50 - 55% of patients with moderate to severe HS do not respond or lose response to Humira

1 combined phase III trial data for Humira: response measured by HiSCR 50 and KOL quotes in LifeSci Capital initiation report 112/2018
The HiSCR as Endpoint Used for Approval in HS

HiSCR – A VALIDATED ENDPOINT

• Humira was approved based on HiSCR response – providing a potential pathway to approval

• HiSCR defines 3 types of lesions:
  – Abscesses
  – Inflammatory nodules
  – Draining fistulas

• HiSCR response defined as:
  – At least 50% reduction in total abscess and inflammatory nodule count (AN count)
  – No increase in the number of abscesses from baseline
  – No increase in the number of draining fistulas from baseline
IFX-1 Open Label Phase IIa Study in Hidradenitis Suppurativa

OBJECTIVE
• Assessing safety and efficacy of IFX-1 in HS
• Primary endpoint: safety
• Secondary endpoint: HiSCR response at different time points,

DESIGN
• Open label
• Single-center
• 12 patients

PATIENT CHARACTERISTICS

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<table>
<thead>
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<tr>
<td>Male</td>
<td>8</td>
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<tr>
<td>(66.7%)</td>
<td></td>
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<tr>
<td>Age [y]</td>
<td>48 ± 15</td>
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<tr>
<td>50 (22; 69)</td>
<td></td>
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<tr>
<td>Hurley Stage III</td>
<td>12</td>
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<tr>
<td>(100%)</td>
<td></td>
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<tr>
<td>BMI</td>
<td>27.3 ± 4.9</td>
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<tr>
<td>26.6 (19.6; 34.5)</td>
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<tr>
<td>Weight [kg]</td>
<td>82.2 ± 14.7</td>
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<tr>
<td>78.0 (63.0; 105.0)</td>
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<tr>
<td>Duration of HS [y]</td>
<td>20 ± 9</td>
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<tr>
<td>20 (3; 35)</td>
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<tr>
<td>AN count</td>
<td>6.4 ± 2.5</td>
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<tr>
<td>6 (3; 11)</td>
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<tr>
<td>Failure to TNF-alpha blockade</td>
<td>9/12</td>
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TREATMENTS
• 1 dose group
• Weekly i.v. 800 mg until week 8 (plus one additional loading dose on day 4)
IFX-1 Open Label Phase IIa Study in Hidradenitis Suppurativa: HiSCR Response

- 83% HiSCR response rate in a severe patient population – with long effect duration
- Strong effect on draining fistula reduction detected (not captured with the HiSCR) – data not shown
Efficacy of IFX-1: Skin Response Example, Phase IIa Trial in HS

IFX-1 demonstrated a long lasting effect on the inflammatory lesions after only 8 weeks of 800mg qw dosing
IFX-1 in HD: SHINE Study Details

**Main Period**
- Placebo
- IFX-1 minimal dose (400mg q4w)
- IFX-1 low dose (800mg q4w)
- IFX-1 medium dose (800mg q2w)
- IFX-1 high dose (1200mg q2w)

**Open Label Extension Period (OLE)**
- Week 16 HiSCR Responders:
  - IFX-1 low dose (800mg q4w)
- Week 16 HiSCR Non-Responders:
  - IFX-1 medium dose (800mg q2w)

**Screening**
16 weeks (double blind)

**TOTAL TREATMENT TIME:** 9 months + 1 month observation

**MAIN GOALS**
- Test a dose dependent effect of IFX-1 on HiSCR responds at week 16 (primary endpoint)
- Assess long term safety of IFX-1
- Test durability of response with lower maintenance therapy in open label extension period

**Important Note:** Patients entering the OLE were not unblinded to their initial therapy
SHINE Study Patient Disposition for Open Label Extension (OLE)

SNAPSHOT ANALYSIS END OF SEP. 2019
- End of Treatment (EOT) - week 40: Sept. 6th 2019 (completed at snapshot: n = 116)
- Last patient last visit (week 44): Oct. 4th 2019
- Final Data will be available early 2020

MAIN PERIOD
- week 16
- OLE Period
- week 40 + 4

Patients Enrolled
n = 179

Patients Dosed
n = 177 (100%)

Entered Extension
n = 156 (88%)

Completed OLE
n = 122 (69%)
- visit at EOT at wk 40
  n = 116
- completed wk 44
  n = 122

Discontinued
n = 34 (19%)
SHINE STUDY: Primary Outcome HiSCR at Week 16 versus AN Count Reduction

**HiSCR response rate (%) week 16***

- Placebo: 47.1
- Minimum: 40.0
- Low: 51.5
- Medium: 38.7
- High: 45.5

* Full analysis set

**AN Count Score change (mean %) week 16***

- Placebo: -26.5
- Minimum: -32.7
- Low: -54.6
- Medium: -44.9
- High: -47.7

*n = approx. 35/ group*

**Primary Endpoint: HiSCR dose response signal not met but signal towards improved AN count**
SHINE STUDY: Outcome on Draining Fistula and IHS-4 Score Reduction – week 16

Stat. significant change in DF and in IHS-4 scores detected

* Full analysis set  ** Full analysis set – baseline adjusted
IHS-4 Score: Includes and Weights All Inflammatory Lesions

Developed by KOL’s / Physicians to establish a new severity scoring system, suitable for tracking treatment response

- Captures reduction of draining fistulas (unlike HiSCR)
- Weights the most fluctuating lesions (infl. nodules) less than abscesses or fistula – lower variability
- Internal validation work shows correlation with DLQI and Pain Scores in SHINE data set

**IHS-4 points = sum of**

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Weight</th>
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<tr>
<td>number of inflammatory nodules</td>
<td>x 1</td>
</tr>
<tr>
<td>number of abscesses</td>
<td>x 2</td>
</tr>
<tr>
<td>number of draining fistulas</td>
<td>x 4</td>
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**HS STAGE**

- **Mild:** ≤ 3 points
- **Moderate:** 4-10 points
- **Severe:** ≥ 11 points
Comparison of HiSCR for Week 16 Responder versus Non-responder Groups (OLE) Over Time

Responders: 71% maintain HiSCR response with low dose IFX-1
Non-responders: 42% become HiSCR responders with medium dose IFX-1

* full analysis set
Inflammatory Lesion Reductions in all OLE Patients at End of Treatment (week 40) Compared to Placebo Group Performance in Main Period

Relative Reduction (% mean) of Counts / Scores compared to Respective Baseline (Day1)*

of all OLE patients on week 40 (n=116)

Marked improvement of all inflammatory lesions over time – not explainable by placebo effect

* full analysis set (unadjusted)
IHS-4 Scores Over Time in OLE: Non-responders versus Responders

Change in IHS-4 scores between week 16 and week 40 in week 16 HiSCR responders versus non-responders*

- **Non-Responders**
  - (n = 84)
  
- **Responders**
  - (n = 72)

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**Non-responders improve under medium dose IFX-1 treatment during OLE**

**Responders are relatively “stable” with their IHS-4 scores on low dose IFX-1**

* full analysis set
IHS-4 Scores in OLE Patients: Relative Change from Baseline (Day 1)
HiSCR Non-responder Group (week 16)

**IHS-4 scores**: Relative change from baseline (mean) in OLE patients at week 16 and week 40 in **HiSCR non-responder patients** (week 16) – displayed per Main Period Treatment group*

Main period placebo and minimal dose patients show strongest improvement in IHS-4 scores when being treated with medium IFX-1 dose (for week 16 HiSCR Non-Responders)

*Last observation carried forward analysis set
IHS-4 Scores in OLE Patients: Relative Change from Baseline (Day 1) HiSCR Responder Group (week 16)

**IHS-4 Scores** relative change to baseline (mean) in OLE patients at week 16 and week 40 in week 16 HiSCR responders - displayed per Main Period Treatment group*

**Treatment Group in Main period:**
- placebo
- 400 mg q4w
- 800 mg q4w
- 800 mg q2w
- 1200 mg q2w

**Main period HiSCR responders maintain or slightly lose their IHS-4 score improvements when treated with the low dose IFX-1**

* Last observation carried forward analysis set
Results indicate that IFX-1 consumption in HS is much higher than in other diseases (trough levels are a multiple lower at same dose)

Results further indicate that this consumption in HS is likely driven by a very high C5a turnover rate

Models suggest a target mediated drug clearance: this means, the higher the generation rate of C5a the higher the IFX-1 clearance

Models suggest that IFX-1 achieves a good tissue penetration rate, especially for higher dose groups
Key Takeaways of SHINE Study:

- HiSCR is burdened by high variability (driven by AN count variability) and by a lack of capturing reduction of draining fistula.

- Evidence for a very high C5a turnover rate in HS, leading to IFX-1 consumption.

- IFX-1 leads to a market reduction of all inflammatory lesions in this disease with a durable long term effect detected even at non-optimal doses.

- IFX-1 long term treatment was well tolerated, no drug related SAE’s in the open label extension phase.
Thank you for your attention

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