Lessons learnt in recent trials in negative symptoms

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ISCTM Paris, September 1st, 2017
Disclosures

• I am an employee of F. Hoffmann – La Roche
• I hold stocks of F. Hoffmann – La Roche, Novartis, and Basilea

• The views and opinions expressed in this presentation only present the personal views of Dr. Umbricht and not those of F. Hoffmann – La Roche, Ltd.
Outline

• Results of a survey among experienced trialists
• Some lessons learnt from the bitopertin phase 3 trials
• Results of a meta-analysis of recent negative symptom trials
• Monotherapy or adjunctive treatment?
Definitions*

• Prominant or dominant negative symptoms
  – High negative symptoms but also a “substantial burden from psychotic symptoms including hallucinations and delusions”
    ÿ Example: A score of ≥4 on at least 3, or ≥5 on at least 2, of the 7 negative subscale items of the Positive and Negative Syndrome Scale (PANSS) (Stauffer et al 2012).

• Predominant negative symptoms
  – High negative symptoms, but mild and stable positive symptoms (and low EPS and depression)
    ÿ Example: A score of ≥4 on at least 3, or ≥5 on at least 2, of the 7 negative subscale items of the Positive and Negative Syndrome Scale plus a PANSS positive score of <19, a Barnes Akathisia score of <2, a Simpson–Angus score of <4, and a Calgary Depressive Scale score of <9 (Stauffer et al 2012)

*Marder et al, 2013
Results of a survey among experienced trialists

- 12 colleagues interviewed
- 8 from industry, 4 from academia
- Responsible for 1-4 trials, average 2, in total 23 trials (9 academia, 14 industry)

**Methods**
- First a questionnaire* was sent out
- Followed up by personal interviews**

*Developed by Nina Schooler, Celso Arango and Daniel Umbricht
**Conducted by Nina Schooler and Daniel Umbricht
Key ‘hot’ topics

• Patient population/Inclusion criteria
• Scales/Assessments
• Role of informant
• Role of a psychosocial «platform» in a trial
Patient population/Inclusion criteria

• **Predominant versus dominant negative symptoms**
  – General agreement that inclusion criteria may have been ‘overengineered’ with too much a focus on keeping positive symptoms low excluding a large number of subjects from studies
  – General agreement that substantial positive symptoms should be allowed as long as they are **stable and not ‘disruptive’**
  – Possible solution: Stratify predominant/dominant neg sx patients

• **Severity of negative symptoms**
  – Concern that including only patients with relatively high negative symptoms selects more ‘treatment resistant’ and least engaged patients
  – Solution: Include patients with **less severe** negative symptoms, stratify by severity

• **Duration of illness**
  – Focus on patients **earlier** in their illness
Effects of neg sx inclusion criteria

- More restrictive baseline symptom severity thresholds yielded a considerably smaller sample size and higher negative and lower positive symptoms at baseline.
- Unadjusted negative symptom change greater with more restrictive criteria;
- When adjusted for baseline severity the magnitude of change comparable across subsets.
- The amount of variance in negative symptom change attributed to positive symptom change also comparable across subsets.

Dunayevich et al, European Neuropsychopharmacology(2014) 24, 1615–1621
Change in neg sx (NSFS*) tends to be greater when positive symptoms are “relatively” lower - independent of negative symptom level**

* NSFS= PANSS Negative Symptom Factor Score (Marder factor; item scoring 0-6))
** Data from phase 3 bitopertin suboptimally controlled symptoms studies
Change in neg sx (NSFS*) tends to be greater when positive symptoms are lower - independent of negative symptom level**

* NSFS= PANSS Negative Symptom Factor Score (Marder factor; item scoring 0-6)
** Data from phase 3 bitopertin suboptimally controlled symptoms studies
Change in positive sx (PNSFS*) tends to be greater when positive symptoms are higher - independent of negative symptom level**

* PSFS= PANSS Positive Symptom Factor Score (Marder factor; item scoring 0-6)
** Data from phase 3 bitopertin suboptimally controlled symptoms studies
IRT analysis, Bitopertin P3 negative sx studies:

Key ‘avolition’ items of PANSS NSFS perform best around or below mean

Analysis supports the view that patients with less severe neg sx should be enrolled

Analysis performed by A. Khan, NeurocogTrials

N=1878

Item information

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N=1878  Item information

NSFS distribution at baseline
IRT analysis of NSA, Bitopertin P3 neg sx studies

N=1783

Item information

NSA Total Score Distribution at baseline

Analysis performed by A. Khan, NeurocogTrials
Individual items of NSA-16 perform the best around or below mean (IRT analysis, Bitopertin P3 neg sx studies)

Prolonged time to respond

Restricted speech quantity

Impoverished speech content

Inarticulate speech

Emotion: Reduced range

Affect: Reduced modulation of intensity

Affect: Reduced display on demand

Reduced social drive

N=1783

Analysis performed by A. Khan, NeurocogTrials

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Individual items of NSA-16 perform the best around or below mean (IRT analysis, Bitopertin P3 neg sx studies)

- Poor rapport with interviewer
- Sexual interest
- Poor grooming and hygiene
- Reduced sense of purpose
- Reduced interests
- Reduced daily activity
- Reduced expressive gestures
- Slowed movements

Analysis performed by A. Khan, NeurocogTrials
Additional topics

Role of Informant
- Deemed unreliable as informant, more important for compliance
- Insistence on informant may limit patients to lower functioning patients, potentially excluding patients who live independently and may respond best

Scales/Assessments
- Include scales that measure **avolition and expressive deficits** separately (CAINS, BNSS), keep PANSS for legacy reason
- Most colleagues in favor of **either centralized ratings, video taping/independent assessment** or ‘Blended’ approaches with site rater responsible for enrollment, CR or videotaped interviews used for outcome
- Some scepticism that CR could not capture all nuances of negative symptoms also expressed

Role of a psychosocial «platform» in a trial
- Biggest difference between academic and industry
  - Colleagues from academia in favor of a psychosocial platform, also to increase number of visits to provide a «low level» psychosocial platform
  - Colleagues from industry were less enthusiastic, favored ‘clean’ studies with fewer visits

Biomarkers
- If biomarkers were considered, **effort-choice tasks** recommended to characterize patients
Drivers of placebo response in negative symptoms trials
Larger Placebo Response in Antipsychotic Trials Obscures True Treatment Effect

Factors associated with placebo response:
- Year of study
- Number of sites
- Percentage of university or VA settings

Placebo Response >40% Obscures Treatment Effect in MDD

Meta-analysis of adjunctive treatment in MDD

Placebo (+SoC) response >40% showed a trend to lower risk ratio of response to the adjunctive drug vs. placebo  (Iovieno & Papaksotas 2012)

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Response* Rates (ITT population) in Bitopertin Phase 2 and Phase 3 Trials in Negative Symptoms of Schizophrenia

* Response defined as ≥ 20% improvement on the NSFS

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**Phase 2 Trial**

- Placebo: 44%
- Bitopertin 10mg: 58%

**Phase 3 Trials**

- Placebo: 55%
- Bitopertin 10mg: 60%

**Comparison**

- Placebo: 35%
- Bitopertin 10mg: 61%
Categorization of patients

Responding to any intervention
- Active +
- Placebo +
- Not informative

Responding to active, but not placebo
- Active +
- Placebo ±
- Informative

Not responding to any intervention
- Active -
- Placebo -
- Not informative

Identify sites that show high or low average placebo response and remove all data including data from patients on active treatment, assuming that average placebo response is indexing category of patients recruited at that site → composition of patients contains more patients in the green group with filter narrowing.
Effect of Sites with “Normal” PBO Response: NS, 10mg, MMRM Week 24, Bitopertin Phase 3 neg sx studies

Results in “Normal” Pbo response sites better than the overall population in all NS studies.
Correlation between Number of Study Sites and Placebo Response* Rates (ITT population) in Bitopertin Phase 2 and Phase 3 Trials in Negative Symptoms of Schizophrenia

* Response defined as ≥ 20% improvement on the NSFS

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Correlation between Number of Study Sites and Placebo Response* Rates (ITT population) in Bitopertin Phase 2 and Phase 3 Trials in Negative Symptoms of Schizophrenia

* Response defined as ≥ 20% improvement on the NSFS
Investigating predictors of placebo response in phase 3 bitopertin neg sx trials

- Erratic ratings
- Change in the first four weeks
Erratic ratings of NSFS in placebo treated patients—change of at least 20% in opposite directions across 2 consecutive visits associated with greater placebo response at patient level.

Analysis performed by A. Kott and X. Wang, Bracket
Erratic ratings of NSFS in placebo treated patients—change of at least 20% in opposite directions across 2 consecutive visits associated with greater placebo response at patient level.

Analysis performed by A. Kott and X. Wang, Bracket.

ES = 0.04
Erratic ratings of NSFS in placebo treated patients - change of at least 20% in opposite directions across 2 consecutive visits associated with greater placebo response at patient level

Protocol NN25310

Analysis performed by A. Kott and X. Wang, Bracket

ES = 0.04
Erratic ratings of NSFS in placebo treated patients – change of at least 20% in opposite directions across 2 consecutive visits associated with greater placebo response at site level*

Protocol WN25308

Study Placebo response (N=199)
Not affected subjects (N=161)
@ 73 sites
Affected subjects (N=38; 19%)
@ 19 sites

ES = 0.11

*sites with at least one patient with erratic ratings in any treatment arm

Analysis performed by A. Kott and X. Wang, Bracket
Erratic ratings of NSFS in placebo treated patients – change of at least 20% in opposite directions across 2 consecutive visits associated with greater placebo response at site level*

Protocol WN25309

- Study Placebo response (N=202)
- Not affected subjects (N=154) @ 72 sites
- Affected subjects (N=48; 23%) @ 24 sites

ES = 0.14

*sites with at least one patient with erratic ratings in any treatment arm

Analysis performed by A. Kott and X. Wang, Bracket
Erratic ratings of NSFS in placebo treated patients – change of at least 20% in opposite directions across 2 consecutive visits associated with greater placebo response at site level*

Protocol NN25310

- Study Placebo response (N=197)
- Not affected subjects (N=152) @ 79 sites
- Affected subjects (N=45; 27%) @ 26 sites

Analysis performed by A. Kott and X. Wang, Bracket

*sites with at least one patient with erratic ratings in any treatment arm
Placebo response – Improvement in NSFS above 95th percentile at week 4 at patient level

Protocol WN25308

Change in Marder Negative Factor Score

LSMean +/- SE

Study week

Study Placebo response (N=199)
Not affected subjects (N=187)
Affected subjects (N=12)

ES = 0.06

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Placebo response – Improvement in NSFS above 95th percentile at week 4 at patient level

Protocol WN25309

Change in Marder Negative Factor Score LSMean +/- SE

Study week

Study Placebo response (N=202)
Not affected subjects (N=195)
Affected subjects (N=7)

ES = 0.09

Analysis performed by A. Kott and X. Wang, Bracket

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Placebo response – Improvement in NSFS above 95th percentile at week 4 at patient level

Protocol NN25310

Change in Marder Negative Factor Score
LSMean +/- SE

Study week

-0.001
<.0001
<.0001
<.0001
<.0001

ES = 0.11

Analysis performed by A. Kott and X. Wang, Bracket

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Placebo response – Improvement in NSFS above 90th percentile at week 4 at site level

Protocol WN25308

- Study Placebo response (N=199)
- Not affected subjects (N=169) @ 75 sites
- Affected subjects (N=30; 15%) @ 17 sites

ES = 0.07

*sites with at least one patient with improvement above 90th percentile in any treatment arm

Analysis performed by A. Kott and X. Wang, Bracket
Placebo response – Improvement in NSFS above 90th percentile at week 4 at site level

Protocol WN25309

Change in Marder Negative Factor Score LS Mean +/- SE

-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0

Study week

0 4 8 12 16 20 24

Study Placebo response (N=202)
Not affected subjects (N=174) @ 77 sites
Affected subjects (N=28; 13%) @ 19 sites

ES = 0.09

* sites with at least one patient with improvement above 90th percentile in any treatment arm

Analysis performed by A. Kott and X. Wang, Bracket

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Placebo response – Improvement in NSFS above 90th percentile at week 4 at site level

Protocol NN25310

- Study Placebo response (N=197)
- Not affected subjects (N=165) @ 91 sites
- Affected subjects (N=32 ;16%) @ 14 sites

Change in Marder Negative Factor Score LSMean +/- SE

Study week

ES = 0.20

*sites with at least one patient with improvement above 90th percentile in any treatment arm

Analysis performed by A. Kott and X. Wang, Bracket
Placebo response – Improvement in NSFS above 90th percentile at week 4 at site level

ES of change in placebo response 0.04 to 0.2 potentially jeopardizing signal detection. These observations raise the issues of patient selection and assessment quality.

- Erratic ratings not compatible with known rate of change in patients
  - Supports the use of centralized or videotaped ratings and/or performance based and ecologically momentary assessments

- Dramatic improvement post randomization not expected in true negative symptom patients
  - Need for biomarkers and behavioral characterization (e.g. Effort choice task)
Meta-regression analysis of placebo response in neg sx trials*

- Eighteen clinical trials (12 academia, 6 industry) conducted in the last 15 years from seventeen publications, assessing the effect of 13 drugs versus placebo on negative symptom in 998 patients on stable AP background treatment.

- Placebo response was significant (p<0.001) and clinically relevant (Cohen’s d: 2.91, 95% CI: 2.05 to 3.77), but there was significant heterogeneity and high risk of publication bias.

- Multivariable meta-regression analysis found that a higher placebo response was significantly and independently associated with:
  - Higher numbers of arms in the trial (p=0.001)
  - More study sites (p<0.001)
  - Industry sponsorship (p=0.001)

- Severity of negative and positive symptoms at baseline were not associated with placebo response when controlling for other factors.

*Fraguas D, Díaz-Caneja CM, Pina-Camacho L, Umbricht D, Arango C: manuscript in preparation
Adjunctive versus monotherapy?
Adjunctive versus monotherapy?

- Proof-of-Mechanism (POM) study, randomized, double-blind, placebo-controlled, three-way crossover design

- Six different treatment sequences (n=5) of PDE10 inhibitor RG7203 at 5 mg QD and 15 mg QD and placebo on top of stable antipsychotic treatment

- N=24 (completers; 33 recruited) Schizophrenia patients with negative symptoms (mild/moderate)

- At end of each treatment period imaging (monetary incentive delay task) and behavioral (effort choice task) assessment of reward anticipation and reward valuation
MID Task: Increased discrimination between reward and non-reward at low dose in the context of an overall blunted activation in drug conditions

Figures show time-dependent fitted BOLD response

Staff activation in healthy volunteers

**PDE10 placebo**

**PDE10 low dose**

**PDE10 high dose**

* two-sided p-value for paired t-test versus placebo

Error areas represent the standard error of mean
Patients choose high effort high reward option significantly less often during treatment than during placebo.

Multiple regression shows that overall activation but not differential activation (reward anticipation versus control) is related to effortful behavior.
Effect of risperidone in healthy volunteers (N=21): Risperidone blunts the overall response in the MID task

Do antipsychotics curtail potential benefits of adjunctive treatments for negative symptoms? In-hous preclinical data would support that

“The preferred design is a double-blind comparison with placebo, especially since no standard treatment for negative symptoms is recognized.....(Möller et al, Working group on negative symptoms in schizophrenia, Psychopharmacology, 1994)
Conclusions

• Patient selection
  – Drop restrictions on level of positive symptoms, as long as they are not ‘disruptive’, and stratification into dominant vs predominant neg symptom patients
  – Consider enrolling patients with moderate negative symptoms (i.e. 14 and up on NSFS [scoring 0-6])
  – Include patients with shorter duration of illness
  – Consider patients who can live independently, that is have more potential for improvement, i.e. consider dropping requirement of informant

• Assessments
  – Consider use of effort choice task to characterize patients
  – Consider centralized or videotaped independent ratings

• Study design/operational aspects
  – Keep site numbers low; in phase 3 consider separate safety studies
  – Keep number of arms to a minimum
  – Consider a monotherapy trial in patients who have predominant negative symptoms?

• Industry versus academic trials? Result of commercialization of drug development? How can we involve academia more?