MCB3681 – a novel narrow-spectrum Gram-positive antibacterial for intravenous treatment of *Clostridium difficile* infections

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ECCMID 25-28 April 2015

The Compound: MCB3681

MCB3681, the active substance of prodrug MCB3837, is being developed as an intravenous (iv.) treatment of *Clostridium difficile* infections (CDI) for which currently no approved iv. treatment option exists. It is a small molecule antibacterial of a novel class with structural elements of an oxazolidinone and a quinolone. MCB3681 affects four different targets resulting in superior antimicrobial activity, exceptionally low propensity for resistance, and lack of cross-resistance to any established class of antibacterials while having an ecologically favorable impact on the human microbiota [1].

Lead Indication: iv. Treatment of CDI

In 2013 *C. difficile* was assigned a threat level of urgent by the U.S. CDC [2]. Incidence of hospitalized patients with CDI is estimated to reach one million in the U.S. and EU by 2021 [3,4]. More than 40% of hospitalized *C. difficile* patients are diagnosed with severe/ severe-complicated CDI (Fig. 5), half of which receive off-label iv. drugs as there is no approved iv. treatment available [3]. This results in a high unmet medical need for an iv. treatment, and MCB3681 is currently the only antibacterial in clinical development for iv. treatment of CDI (Table 1).

Antibacterial	Routes	Phase	MIC range mg/L
MCB 3681	**iv.**	**Phase I**	**0.008 – 0.5**
Metronidazole	iv. / oral	**off-label**	0.125 – 2
Vancomycin	Oral	Market	0.125 – 1
Fidaxomicin	Oral	Market	0.008 – 0.125
Tigecycline	iv.	**off-label**	0.032 – 0.1
Cadazolid	Oral	Phase III	0.064 – 0.5
Surotomycin	Oral	Phase III	<0.125 – 2
LFF571	Oral	Phase II	0.125 – 0.5
SMT19969	Oral	Phase II	0.125 – 0.5
CRS3123	Oral	Phase I	0.5 – 1

Table 1: Overview of antibacterial treatments marketed and in development for CDI [3,4]

Fig. 1: **Viable counts of clostridiae**

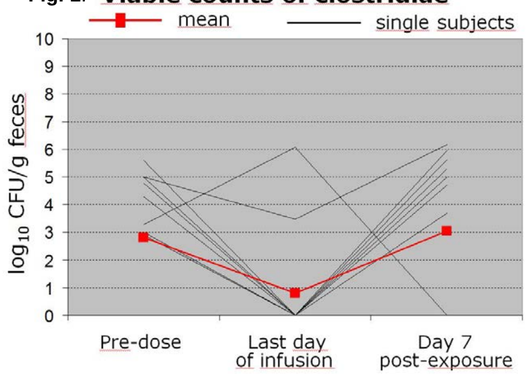


Fig. 2: **Viable counts of bacteroides**

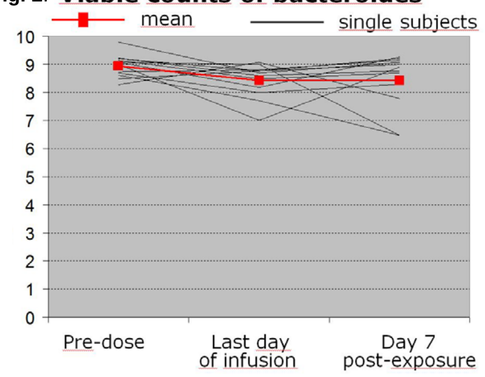


Fig. 3: **Fecal concentrations of MCB3681** (mean ± SD; n=12)

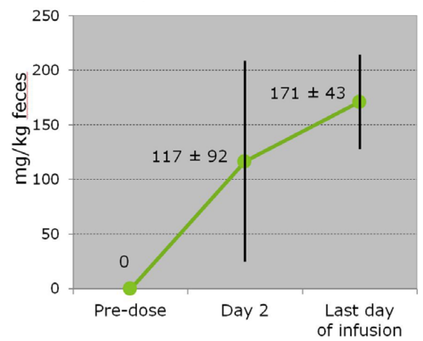


Fig. 4: **Activity against *C. difficile*** (MIC_{90}, range; 114 clinical isolates)

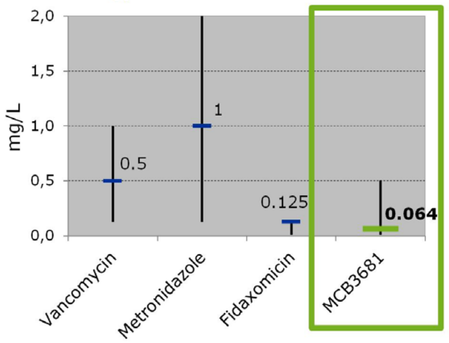
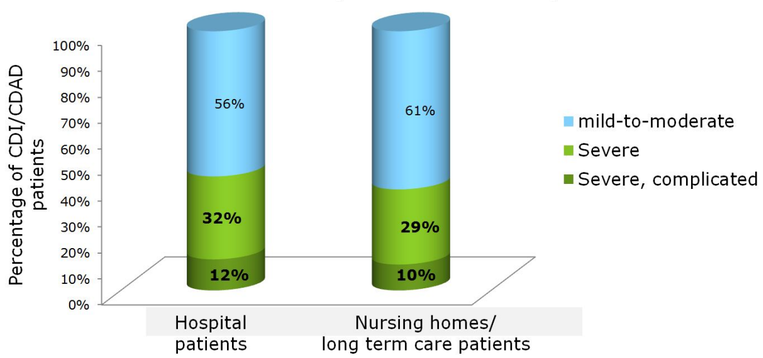


Fig. 5: ***C. difficile* infections by disease severity**



Proof of Principle in Phase I

Reduction of fecal Gram-positives while sparing Gram-negatives

In a phase I b study at Karolinska Institute, an antibacterial effect on Gram-positive species in feces (Fig. 1) was demonstrated in 12 healthy subjects without affecting aerobic and anaerobic Gram-negative species incl. Bacteroides (Fig. 2) in the intestine, known to provide colonization resistance in the gut [1].

High fecal concentrations of MCB3681

Fecal concentrations of MCB3681 in 12 healthy subjects ranged from 99 to 226 mg/kg feces [1] (Fig. 3).

Strong activity against *C. difficile* strains

MCB3681 has shown strong in-vitro activity against 114 clinical isolates of *C. difficile* (Fig. 4) showing superior activity compared to vancomycin, metronizadole, fidaxomicin, and other comparators [5].

Safety Profile

Safety and tolerability of MCB3837 (prodrug of MCB3681) have been demonstrated in almost 100 healthy volunteers in three phase I studies including a multiple dose phase I b study with daily infusions of 6 mg/kg MCB3837 for 5 days [1].

Next Steps

Based on the proof of principle and a superior in-vitro activity compared to existing CDI treatments as well as a favorable clinical safety profile [1,5,6], Morphochem is currently planning Phase II/ III clinical development for iv. treatment of CDI.

Company Profile

Morphochem AG is a privately held company located in Munich, Germany; it is a 100% subsidiary of Biovertis AG, Austria, backed by TVM Capital. Its mission is to develop and commercialize a novel class antibacterial to treat serious *C. difficile* infections that pose an urgent threat to public health. (Contact: thomas.kapsner@biovertis.de)

Sources & Publications

[1] Rashid M et al., Nord CE: Ecological impact of MCB3837, IJAA 44 (2014) 44, 125-130
[2] CDC (U.S.A.): Antibiotic Resistance Threats in the U.S., 2013
[3] Decision Resources: Treatment Trends C. diff. Infections, 2013
[4] Morphochem Analysis, 2015
[5] Rashid M et al., Nord CE: In vitro activity of MCB3681 against C. diff., Anaerobe 28 (2014) 216-219
[6] Dalhoff A, Weintraub A, Nord CE: Alternative Strategies for Proof-of-Principle, AAC 58 (2014) 4257-4263