BAN2401 shows stronger binding to soluble aggregated amyloid-beta species than aducanumab

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Objectives: To examine if there are differences in binding characteristics between BAN2401, an antibody continuing in development in phase 3, and aducanumab, an antibody which met futility in phase 3, to better understand the differences in mechanism of action.

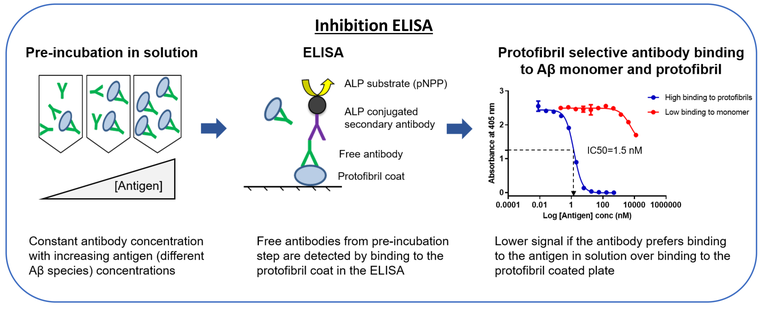
Conclusion: Compared to aducanumab, BAN2401 showed up to 100 times stronger *in vitro* binding to Aβ protofibrils. The stronger binding of BAN2401 to these toxic Aβ species may mediate the differences in clinical responses observed between the two antibodies.

Background

The development of several monoclonal antibodies targeting amyloid-β (Aβ) has been discontinued due to lack of efficacy and/or adverse events. There has been an increasing interest in soluble aggregated Aβ species, *i.e.* oligomers (<75 kDa) and protofibrils (>75 kDa), as key pathogenic species. We examined the binding characteristics of BAN2401 and aducanumab to better understand the differences in their mechanism of action. BAN2401 was designed and generated to specifically bind soluble aggregated Aβ species.

Material & Methods

Inhibition ELISA and Surface Plasmon Resonance (SPR, Biacore) were used to investigate binding of BAN2401 and aducanumab to oligomers and to small and large protofibrils, as determined by size exclusion chromatography (SEC).
Protofibrils were defined as soluble aggregated Aβ species, >75 kDa, which do not pellet during 16000 *x g* centrifugation. Oligomers, defined as <75 kDa, were isolated using a Superdex 75 PC 3.2 column.
In SPR, the monomer affinities were determined by injecting monomers over captured antibodies. For protofibrils and fibrils, the antibodies were injected over immobilized Aβ species.



Results

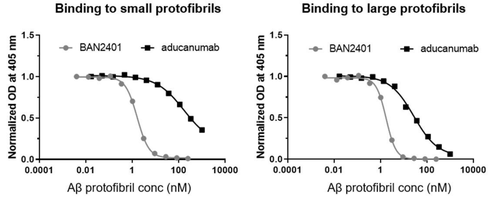
Inhibition ELISA

BAN2401 exhibited similar binding strength to both small (IC50=1.6 nM) and large (IC50=1.7 nM) Aβ protofibrils, whereas the binding of aducanumab to both species was significantly weaker (IC50=171 nM and 27 nM, respectively). Thus, BAN2401 binds up to 100 times stronger to Aβ protofibrils, as compared with aducanumab. In addition, BAN2401 showed strong binding to cross-linked oligomers (<75 kDa), whereas only very weak binding was observed to these species with aducanumab.

Biacore

Interaction analysis of BAN2401 and aducanumab to protofibrils by SPR (Biacore) confirmed data from inhibition ELISA. Compared with aducanumab, BAN2401 exhibited stronger binding to protofibrils. Both antibodies had fast on-rates but BAN2401 had a considerably slower off-rate. Both antibodies showed very weak binding to monomers.

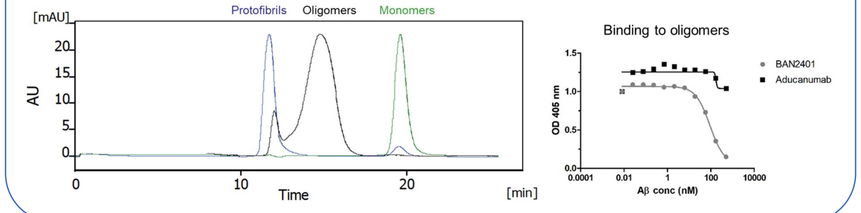
BAN2401 showed stronger binding than aducanumab to both small and large protofibrils by inhibition ELISA



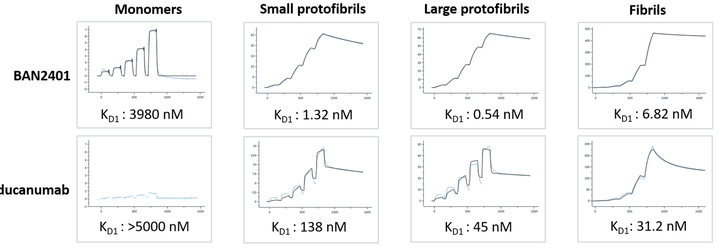
Antibody	IC50 (nM)
BAN2401	1.6
aducanumab	171.1
Fold difference	≈100

Antibody	IC50 (nM)
BAN2401	1.7
aducanumab	27.2
Fold difference	16

BAN2401 demonstrated stronger binding than aducanumab to cross-linked Aβ oligomers (<75 kDa) by inhibition ELISA



BAN2401 showed much stronger binding than aducanumab to soluble aggregated Aβ species by SPR



References

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