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| **Table 2: Clinical efficacy trials of cariprazine in schizophrenia**  |
| **Identifier** | **Reference** | **Cariprazine dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in cariprazine group relative to comparator group** | **Effect size** |
| NCT04578756 |  | Cariprazine (dose not stated) | No comparator group | SCZ and bipolar  | Children and adolescents 10-18 years | Open label flexible dose study, phase III | Incidence of AEs | 200 planned | 26 weeks | Planned | USA | 2020 – 2023 (est.) | Results due 2023 |
| NCT03817502 |  | Cariprazine 1.5mg, 4.5mg | Placebo | SCZ | Adolescents 13-17 years | Double blinded RCT, phase III | Change from baseline in PANSS total score | 330 planned | 6 weeks | In progress | USA, Russia & Eastern Europe  | 2019 – 2022 (est.) | Results due 2022 |
| NCT03593213 |  | Cariprazine 3mg, 4.5mg | Placebo | SCZ | PANSS ≥70 and ≤ 120 | Double blinded RCT, phase III | Time from baseline to first relapse date | 572 | 30 weeks | Terminated | USA, Asia, Eastern Europe & Central America  | 2018-2021 | Study terminated: FDA released drug company from its post-marketing requirement |
|  | (Smulevich, Ivanov et al. 2020) | Cariprazine 1.5 – 6mg | No comparator group | SCZ | Predominant negative symptoms  | Observational open-label study | Change in PANSS-NS and CAINS | 60 | 4 weeks | Completed | Russia | 2020 | N/A | Mean change from baseline -4.3 in PANSS-NS (p<0.05) and -4.9 in CAINS (p<0.05)  |
|  | (Rancans, Dombi et al. 2021) | Cariprazine 1.5 - 6mg  | No comparator group | SCZ | Outpatients with negative symptoms | Observational open label study | Change in SAND | 116 | 16 weeks | Completed | Latvia | 2018-2020 | N/A | Mean change from baseline -7.3 (p<0.001) over 16 weeks |
|  | (Németh, Laszlovszky et al. 2017) | Cariprazine 3mg, 4.5mg or 6mg | Risperidone 3mg, 4mg or 6mg | SCZ with persistent negative symptoms | Chronic, stable SCZ  | Double blinded RCT, phase III | Change in PANSS- factor score for negative symptoms  | 461 | 26 weeks  | Completed | Europe & Russia | 2016 | ↑ | Cariprazine vs risperidone: Mean difference -1.46, p=0.002, effect size 0.31 |
| NCT01412060 | (Durgam, Earley et al. 2016) | Cariprazine 3, 6 and 9mg | Placebo | SCZ | PANSS ≥ 70 | Open label-phase (20 weeks) followed by randomised parallel-group study, phase III | Time to the first symptom relapse | 765 in open label phase, 200 in double-blind phase | 72 weeks | Completed | USA, India, & Eastern Europe | 2011-2014 | ↑ | Cariprazine 224 days, placebo 92 daysHazard ratio 0.45, p=0.001Relapse in 47.5% of placebo group vs 24.8% of cariprazine group |
| NCT00404573 | (Durgam, Litman et al. 2016) | Cariprazine 1.5-4.5mg, cariprazine 6-12mg,  | Placebo | SCZ | Acute relapse  | Double blinded RCT, phase III | Change in PANSS total score  | 392 | 6 weeks | Completed | USA | 2006-2007 | ↔ | No significant differences between comparator groups after correction for multiple comparisons.  |
| NCT01104792 | (Nasrallah, Earley et al. 2017) | Cariprazine 3mg, 4.5mg, 6mg, 9mg | No comparator group | SCZ | Stable schizophrenia, diagnosis > 1 year | Open label study, phase III | Change in PANSS total score | 752 | 48 weeks | Completed | USA, South America, Eastern Europe & Asia | 2010 - 2013 | N/A | Mean change from baseline -5.0 over 48 weeks |
| NCT01104766 | (Durgam, Cutler et al. 2015) | Cariprazine 3mg, cariprazine 6mg | Aripiprazole 10mg,placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 617 | 6 weeks  | Completed | USA, Russia & Eastern Europe  | 2010 - 2011 |  ↑ vs placebo↔ vs aripiprazole | Cariprazine 3mg vs placebo: mean difference -6, p=0.004Cariprazine 6mg vs placebo: mean difference -8.8, p<0.001Aripiprazole 10mg/day vs placebo: mean difference -7.0, p<0.001 |
| NCT01104779 | (Kane, Zukin et al. 2015) | Cariprazine 3-6mg, cariprazine 6-9mg | Placebo | SCZ | Acute relapse  | Double blinded RCT, phase III | Change in PANSS total score | 446 | 6 weeks  | Completed | USA, South America, Asia & Africa | 2010 - 2011 | ↑ | Cariprazine 3-6mg vs placebo: mean difference -6.8, p=0.003Cariprazine 6-9mg vs placebo: mean difference -9.9, p<0.001. |
| NCT00694707 | (Durgam, Starace et al. 2014) | Cariprazine 1.5mg, cariprazine 3mg, cariprazine 4.5mg | Risperidone 4mg, placebo | SCZ | Acute relapse | Double blinded RCT, phase II | Change in PANSS total score  | 732 | 6 weeks  | Completed | USA, Asia & Eastern Europe  | 2008 - 2009 | ↑ vs placebo | Cariprazine 1.5mg vs placebo: mean difference -7.6, p<0.001Cariprazine 3mg vs placebo: mean difference -8.8, p<0.001Cariprazine 4.5mg vs placebo: mean difference -10.4, p<0.001Risperidone vs placebo: mean difference -15.1, p<0.001 |
|  | **Key to abbreviations and symbols:**SCZ: SchizophreniaRCT: Randomised controlled trialAE: Adverse eventsPANSS: Positive and negative symptom scaleFDA: United States Food and Drug AdministrationSAND: Short Assessment of Negative DomainsPANSS-NS: Positive and negative symptom scale, Negative subscaleCAINS: Clinical Assessment Interview for Negative Symptoms↑: Better outcome in cariprazine group relative to comparator group (statistically significant)↓: Poorer outcome in cariprazine group relative to comparator group (statistically significant)↔: No statistically significant difference between cariprazine and comparator groups |

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| **Table 3: Clinical efficacy trials of brexpiprazole in schizophrenia**  |
| **Identifier** | **Reference** | **Brexpiprazole dose(s)** | **Comparator group (s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location** | **Year** | **Results** |
|  |  |  |  |  |  |  |  |  |  |  |  |  | **Change in brexpiprazole group relative to comparator group** | **Effect size** |
| NCT04641780 |  | Brexpiprazole 2 – 4mg (for SCZ) | No comparator group | SCZMDD  |  | Prospective cohort study, phase III | Incidence of AEs | 300 planned | 8 weeks  | Recruiting | Philippines | 2019 – 2024 (est) | Due 2024 |
| NCT03238326 |  | Brexpiprazole 1-4mg  | No comparator group | SCZ | Adolescents aged 13 - 17 | Open label study, phase III | Frequency and severity of AEs | 350 planned | Up to 24 months | Recruiting | USA | 2017 – 2023 (est) | Due 2023 |
| NCT03526354 |  | Brexpiprazole 4mg  | Treatment as usual | Co-morbid SCZ and and substance misuse disorder | Psychiatrically stable | Open label RCT, phase IV | Number of days of substance use, change in visual analogue scale measure for craving | 80 planned | 12 weeks | Recruiting | USA | 2018 – 2022 (est) | Due 2022 |
| NCT03874494 |  | Brexpiprazole 2-4mg | Aripiprazole 10-20mg | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 370 planned | 6 weeks  | Recruiting  | China | 2019 – 2021 (est) | Due 2021 |
| NCT03198078 |  | Brexpiprazole 2-4mg,  | Aripiprazole 10-20mgPlacebo | SCZ | Adolescents 13-17 years | Double blinded RCT, phase III | Change in PANSS total score | 480 planned | 6 weeks | Recruiting | USA | 2017 – 2021 (est) | Due 2021 |
| NCT01810783 | (Hakala, Gislum et al. 2018) | Brexpiprazole 1-4mg  | No comparator group | SCZ | Clinically stable | Open label, phase III | Frequency of AEs | 210 | 52 weeks | Completed | USA, Eastern Europe | 2013 - 2017 | N/A | Mean change in PANSS total from baseline to week 52 was -6.8 (95% CI -9.3, -4.2) |
| NCT01397786“ZENITH trial” | (Forbes, Hobart et al. 2018) | Brexpiprazole 1-4mg | No comparator group | SCZ | Outpatients | Open label phase III | Frequency of AEs | 1072 | 52 weeks | Completed | North America, South America, Europe, Asia | 2011-2017 | N/A | Mean change in PANSS total from baseline to week 52 was -12.2. |
| NCT01668797“EQUATOR trial” | (Fleischhacker, Hobart et al. 2017) | Brexpiprazole 1-4mg | Placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Time from randomisation to relapse  | 524 | 52 weeks | Completed | North America, South America, Asia & Eastern Europe  | 2012 - 2015 | ↑ | Time to impending relapse delayed with brexpiprazole treatment compared with placebo (p<0.01). Hazard ratio of 0.292. |
|  | (Ishigooka, Iwashita et al. 2018) | Brexpiprazole 1mg, 2mg, 4mg | Placebo | SCZ | Acute relapse  | Double blinded RCT, phase II/III | Change in PANSS total score | 459 | 6 weeks | Completed | Japan | 2011-2015 | ↑ for brexpiprazole 2mg only | Brexpiprazole 1mg vs placebo: mean difference -0.63, p=0.83Brexpiprazole 2mg vs placebo: mean difference -7.32, p=0.01Brexpiprazole 4mg vs placebo: mean difference -3.86, p=0.20 |
| NCT02054702 | (Citrome, Ota et al. 2016) | Brexpiprazole 3mg  | Aripiprazole 15mg | SCZ | Acute relapse | Randomised open label study, phase II | Change in PANSS total score | 97 | 6 weeks | Completed | USA | 2014 | ↔ | Mean reduction in PANSS total score -22.9 for brexpiprazole (p<0.0001 vs baseline) and -19.4 (p<0.0001 vs baseline) for aripiprazole  |
| NCT01810380“Lighthouse trial” | (Marder, Eriksson et al. 2020) | Brexpiprazole 2-4mg | Quetiapine extended release 400-800mg,Placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 468 | 6 weeks | Completed | USA | 2013-2014 | ↓ | Brexpiprazole vs placebo: mean difference -4.1, p=0.056Quetiapine vs placebo: mean difference -8.0, p<0.01 |
| NCT02013622 | (ClinicalTrials.gov 2016) | Brexpiprazole 1-4mg | No comparator group | SCZ | Early episode SCZ | Open label study, phase III | Change in PANSS total score | 49  | 16 weeks  | Completed | USA | 2013- 2014 | N/A | Mean change in PANSS from baseline -10.2 (p<0.01). |
| NCT01396421“VECTOR trial” | (Correll, Skuban et al. 2015) | Brexpiprazole 0.25mg, 2mg, 4mg | Placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 623 | 6 weeks | Completed | North America, Eastern Europe & Asia | 2011-2013 | ↑ for brexpiprazole 2mg and 4mg | Brexpiprazole 0.25mg vs placebo: mean difference -2.89, p=0.30Brexpiprazole 2mg vs placebo: mean difference -8.72, p<0.01Brexpiprazole 4mg vs placebo: mean difference -7.64, p<0.01 |
| NCT01393613“BEACON trial” | (Kane, Skuban et al. 2015) | Brexpiprazole 1mg, 2mg, 4mg | Placebo | SCZ | Acute relapse  | Double blinded RCT, phase III | Change in PANSS total score | 674 | 6 weeks | Completed | USA, Central America, South America, Eastern Europe & Asia | 2011 - 2014 | ↑ for brexpiprazole 4mg only | Brexpiprazole 1mg vs placebo: mean difference -3.37, p=0.16Brexpiprazole 2mg vs placebo: mean difference -3.08, p=0.14Brexpiprazole 4mg vs placebo: mean difference -6.47, p<0.01.  |
| NCT00905307; STEP 203 | (Correll, Skuban et al. 2016) | Brexpiprazole 0.25mg, 1mg, 2.5mg, 5mg | Aripiprazole 15mgPlacebo | SCZ | Acute relapse | Double blinded RCT, phase II | Change in PANSS total score  | 459 | 6 weeks | Completed | USA, Asia & Europe | 2009 - 2010 | ↔ | Brexpiprazole 0.25mg vs placebo: mean difference 4.88, p=0.23Brexpiprazole 1mg vs placebo: mean difference -4.69, p=0.13Brexpiprazole 2.5mg vs placebo: mean difference -1.72, p=0.58Brexpiprazole 5mg vs placebo: mean difference -4.45, p=0.15Aripiprazole 15mg vs placebo: mean difference -3.68, p=0.31 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaMDD: Major depressive disorderAEs: Adverse eventsPANSS: Positive and negative symptom scaleRCT: Randomised controlled trial CI: Confidence interval ↑: Better outcome in brexpiprazole group relative to comparator group (statistically significant)↓: Poorer outcome in brexpiprazole group relative to comparator group (statistically significant)↔: No statistically significant difference between brexpiprazole and comparator groups |

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| **Table 4: Clinical efficacy trials of brilaroxazine in schizophrenia**  |
| **Identifier** | **Reference** | **Brilaroxazine dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in brilaroxazine group relative to comparator group** | **Effect size** |
| NCT01490086 | (Cantillon, Prakash et al. 2017) | Brilaroxazine 15mg, 30mg, 50mg  | Aripiprazole 15mg, placebo | SCZ or SZA | Acute relapse | Double blinded RCT, phase II | Change in PANSS score | 234 | 28 days  | Completed | North America, Europe & Asia  | 2011-2015 | ↑ | Brilaroxazine 15mg vs placebo: mean difference -8.82, p=0.021Brilaroxazine 30mg vs placebo: mean difference -4.01, p=0.273Brilaroxazine 50mg vs placebo: mean difference -7.8, p=0.016Aripiprazole 15mg/day vs placebo: mean difference +2.09, p=0.556 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaSZA: Schizoaffective disorderRCT: Randomised controlled trialAE: Adverse events↑: Better outcome in brilaroxazine group relative to comparator group (statistically significant)↓: Poorer outcome in brilaroxazine group relative to comparator group (statistically significant)↔: No statistically significant difference between brilaroxazine and comparator groups |

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| **Table 5: Clinical efficacy trials of lumateperone in schizophrenia**  |
| **Identifier** | **Reference** | **Lumateperone dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in lumateperone group relative to comparator group** | **Effect size** |
| NCT04779177 |  | Lumateperone 42mg, 28mg  | No comparator group | SCZ or SZA | Adolescents aged 13-17 years, clinically stable | Open label study, phase I | Pharmacokinetic data, frequency of AEs | 12 planned | 5 days | Planned | USA | March- Oct 2021 (est.) | Due October 2021 |
| NCT04709224 |  | Lumateperone tosylate 50mg, 100mg, 200mg long-acting injection | No comparator group | SCZ | Clinically stable | Open label study, phase I | Pharmacokinetic data, frequency of AEs | 24 planned | Single dose long-acting injection | In progress | USA | 2020-2021 (est.) | Due December 2021 |
| NCT03817528 |  | Lumateperone tosylate 40-60mg  | N No comparator group | SCZ | Inadequate response or tolerability to previous antipsychotics | Open label study, phase II | Change in PANSS total score | 40 planned | 6 months | Terminated | USA | 2019-2021 (est.) | Terminated 2021: Lumateperone approved by FDA |
| ITI-007-303 | (Correll, Davis et al. 2020) | Lumateperone 42mg (lumateperone tosylate 60mg) | No comparator group | SCZ | Clinically stable outpatients | Open label safety study, phase III | Incidence of AEs | 302  | 6 weeks  | Completed | USA | 2017-2018 | N/A | At day 42, mean change in PANSS from previous antipsychotic baseline was -2.2 (p<0.001) |
| NCT02469155; ITI-007-302 | (Vanover, Dmitrienko et al. 2018) | Lumateperone tosylate 20mg, 60mg | Risperidone 4mg,Placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 696 | 6 weeks | Completed | USA  | 2015- 2016 | ↔ | Lumateperone tosylate 20mg vs placebo: mean difference 0.1, p>0.05Lumateperone tosylate 60mg vs placebo: mean difference 0.5, p>0.05Risperidone 4mg vs placebo: mean difference -5.4, p<0.05 |
| NCT02282761; ITI-007-301 | (Correll, Davis et al. 2020) | Lumateperone tosylate 40mg, 60mg  | Placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 450 | 28 days  | Completed | USA  | 2014-2015 | ↑ for lumateperone 60mg only | Lumateperone tosylate 40mg vs placebo: mean difference -2.6, p=0.16Lumateperone tosylate 60mg vs placebo: mean difference -4.2, p=0.02 |
| NCT01499563; ITI-007-005 | (Lieberman, Davis et al. 2016) | Lumateperone 60mg, 120mg | Risperidone 4mg, placebo | SCZ | Acute relapse | Double blinded RCT, phase II | Change in PANSS total score | 335 | 28 days  | Completed | USA  | 2011-2013 | ↑ for lumateperone 60mg only↔ vs risperidone | Lumateperone 60mg vs placebo: mean difference -5.8, p=0.017Lumateperone 120mg vs placebo: mean difference -0.9, p=0.71Risperidone 4mg vs placebo: mean difference -6.0, p=0.013 |
| **Key to abbreviations and symbols:** SCZ: SchizophreniaSZA: Schizoaffective disorderCGI-S: Clinical Global Impression- Severity scoreRCT: Randomised controlled trialPANSS: Positive and negative symptom scaleFDA: United States Food and Drug AdministrationAEs: Adverse events↑: Better outcome in lumateperone group relative to comparator group (statistically significant)↓: Poorer outcome in lumateperone group relative to comparator group (statistically significant)↔: No statistically significant difference between lumateperone and comparator groups |

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| **Table 6: Clinical efficacy trials of F17464 in schizophrenia**  |
| **Identifier** | **Reference** | **F17464 dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in F17464 group relative to comparator group** | **Effect size** |
| NCT02151656 | (Bitter, Istvan, Lieberman et al. 2019) | F17464 20mg BD | Placebo | SCZ | Acute relapse | Double-blinded RCT, phase II | Change in PANSS total score | 134 | 6 weeks | Completed | Europe | 2014-2015 | ↑ | F17464 40mg vs placebo: mean difference -6.2, p<0.01 [one-sided test] |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaSZA: Schizoaffective disorderRCT: Randomised controlled trialAE: Adverse events↑: Better outcome in F17464 group relative to comparator group (statistically significant)↓: Poorer outcome in F17464 group relative to comparator group (statistically significant)↔: No statistically significant difference between F17464 and comparator groups |

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| **Table 7: Clinical efficacy trials of Lu AF35700 in schizophrenia**  |
| **Identifier** | **Reference** | **Lu AF35700 dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in Lu AF35700 group relative to comparator group** | **Effect size** |
| NCT03230864(Anew) |  | Lu AF35700 10mg  | Risperidone 4-6mg, olanzapine 15-20mg | SCZ | Treatment- resistant  | Double blinded RCT, phase III | Change in PANSS score | 119 | 8 weeks | Completed | North America, Europe, Asia  | 2017-2019 | ↔ | Lu AF35700 10mg vs risperidone/olanzapine: mean difference +5.47, p=0.081 |
| NCT02717195(Daybreak) |  | Lu AF3570010mg, 20mg | Risperidone 4-6mg, olanzapine 15-20mg  | SCZ | Treatment-resistant | Double blinded RCT, phase III | Change in PANSS score | 1098 | 10 weeks | Completed | North America, Europe  | 2016-2018 | ↔ | Lu AF35700 10mg vs risperidone/olanzapine: mean difference -0.12, p=0.920Lu AF35700 20mg vs risperidone/olanzapine: mean difference +1.67, p=0.147 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaRCT: Randomised controlled trialPANSS: Positive and Negative Syndrome Scale AE: Adverse events↑: Better outcome in Lu AF35700 group relative to comparator group (statistically significant)↓: Poorer outcome in Lu AF35700 group relative to comparator group (statistically significant)↔: No statistically significant difference between Lu AF35700 and comparator groups |

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| **Table 8: Clinical efficacy trials of pimavanserin in schizophrenia**  |
| **Identifier** | **Reference** | **Pimavanserin dose(s)** | **Comparator groups**  | **Indication** | **Patient group** | **Type of study, phase** | **Primary Outcome Measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in pimavanserin group relative to comparator group** | **Effect size** |
| NCT03121586(ACP-103-035) | (ACADIA Pharmaceuticals Inc 2020d) | Adjunctive pimavanserin 10, 20 or 34mg + usual antipsychotic  | No comparator group | SCZ | Clinically stable  | Open label study, phase III  | Safety and tolerability | 500 planned | 52 weeks | Recruiting | North America, Europe | 2024 (est.) | Due March 2024 |
| NCT04531982 |  | Adjunctive pimavanserin 34mg + usual antipsychotic | Placebo + usual antipsychotic | SCZ | Clinically stable | Double blinded RCT, phase III | Change in NSA-16 total score | 462 planned | 26 weeks | Recruiting | Europe, Russia  | 2020- 2023 (est.) | Due March 2023 |
| NCT03994965 | (Baltzersen, Meltzer et al. 2020) | Pimavanserin 34mg | No comparator group | SCZ spectrum1 | Medication free, first episode psychosis  | Open label study | Change in PANNS total score | 40 planned | 6 weeks | Recruiting | Europe | 2023 (est.) | Due January 2023 |
| NCT02970305(ACP-103-038) | Press release only(ACADIA Pharmaceuticals Inc 2020c, ACADIA Pharmaceuticals Inc 2019) | Adjunctive pimavanserin 10, 20 or 34mg + usual antipsychotic  | Placebo and background antipsychotic  | SCZ | Predominant negative symptoms | Double blinded RCT, phase II | Change in NSA-16 total score | 403 | 26 weeks | Complete, awaiting full publication of results | North America, Eastern Europe | 2016 - 2019 | ↑ | Change in NSA at 26 weeks: mean difference -1.9, p=0.043 |
| NCT02970292(ACP-103-034)(ENHANCE-1) | Report on clinicaltrials.gov + press release(ACADIA Pharmaceuticals Inc 2020a, ACADIA Pharmaceuticals Inc 2020b) | Adjunctive pimavanserin 10, 20 or 34mg + usual antipsychotic  | Placebo + usual antipsychotic  | SCZ | Partial responders | Double blinded RCT, phase III | Change in PANSS total score | 396 | 6 weeks | Complete | North America, Eastern Europe | 2016 - 2019 | ↔ | Change in PANSS: mean difference -1.9, p=0.094  |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaRCT: Randomised controlled trialNSA-16: Negative Symptom Assessment-16 AEs: Adverse eventsPANSS: Positive and negative symptom scale1Schizophrenia, persistent delusional disorder, acute and transient psychotic disorders, schizoaffective disorder, other non-organic psychotic disorders and unspecified non-organic disorders↑: Better outcome in pimavanserin group relative to comparator group (statistically significant)↓: Poorer outcome in pimavanserin group relative to comparator group (statistically significant)↔: No statistically significant difference between pimavanserin and comparator groups |

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| **Table 9: Clinical efficacy trials of roluperidone in schizophrenia**  |
| **Identifier** | **Reference** | **Roluperidone dose(s)** | **Comparator groups**  | **Indication** | **Patient group** | **Type of study, phase** | **Primary Outcome Measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in roluperidone group relative to comparator group** | **Effect size** |
| NCT03397134MIN-101C07 | Not published in peer-reviewed journal, preliminary results accessed from (Minerva Neurosciences Inc 2020)(Minerva Neurosciences Inc 2020)(Minerva Neurosciences Inc 2020) (Minerva Neurosciences Inc 2020) | Roluperidone 32mg, 64mg   | Placebo  | SCZ | Clinically stable | Double blinded RCT, phase III | PANSS negative symptom factor | 514 | 12 weeks, followed by 40-week open-label extension | 12-week study complete but unpublished. 40-week open label not yet complete. | USA, Eastern Europe | 2017-2020 | ↔ | No significant benefit of either dose at 12 weeks. See text for secondary outcomes (change in negative symptom factor -4.3 for roluperidone versus -3.5 for placebo) |
| EudraCT-2014-004878-42MIN-101C03 | (Davidson, Saoud et al. 2017) | Roluperidone 32mg, 64mg  | Placebo  | SCZ | Clinically stable with negative symptoms | Double blinded RCT, phase II | PANSS negative symptom factor | 244 | 12 weeks | Complete | Eastern Europe | 2014-2016 | ↑ | Roluperidone 64mg vs placebo: mean difference -1.97, p ≤0.01Roluperidone 32mg vs placebo:mean difference -1.54, p ≤0.05 |
| NCT00861796CYR-101C01 | Unpublished, but reported in review by(Ebdrup, Bjørn H., Rasmussen et al. 2011).   | Roluperidone 64mg  | Placebo  | SCZ or SZA | Total PANSS>60;CGI>4. | Double blinded RCT, phase II | Total PANSS | 100 | Primary end-point 4 weeks but treatment continued for 12 weeks | Complete | France | 2008-2010 | ↔ | Roluperidone vs placebo: mean difference -3, p=0.06 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaSZA: Schizoaffective disorderRCT: Randomised controlled trial PANSS: Positive and negative symptom scaleCGI: Clinical Global Impression↑: Better outcome in roluperidone group relative to comparator group (statistically significant)↓: Poorer outcome in roluperidone group relative to comparator group (statistically significant)↔: No statistically significant difference between roluperidone and comparator groups |

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| **Table 10: Clinical efficacy trials of ulotaront (SEP-363856) in schizophrenia**  |
| **Identifier** | **Reference** | **Ulotaront dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location** | **Year** | **Results** |
| **Change in ulotaront group relative to comparator group** | **Effect size** |
| NCT04109950 |  | Ulotaront 25mg, 50mg, 75mg, 100mg | No comparator group | SCZ | Acute relapse,  | Open-label extension study, phase III | Incidence of AEs and SAEs | 555 planned | 52 weeks | In progress | USA, Eastern Europe & Russia   | 2019- 2022 (est.) | Due 2022 |
| NCT04115319 |  | Ulotaront 50mg – 100mg  | Quetiapine 400-800 mg  | SCZ | Clinically stable | Double blinded flexible-dose RCT, phase III | Incidence of AEs and SAEs | 300 planned | 52 weeks | In progress | USA, Eastern Europe & Russia | 2019-2022 (est.) | Due 2022 |
| NCT04092686 |  | Ulotaront 75mg, 100mg | Placebo | SCZ | Acute relapse | Double blinded RCT, phase III | Change in PANSS total score | 462 planned | 6 weeks | In progress | USA, Eastern Europe & Russia  | 2019 – 2021 (est.) | Due 2021 |
| NCT04072354 |  | Ulotaront50mg, 75mg | Placebo | SCZ | Acute relapse  | Double blinded RCT, phase III | Change in PANSS total score | 525 planned | 6 weeks | In progress | USA, Eastern Europe & Russia  | 2019- 2021 (est.) | Due 2021 |
| NCT04038957 |  | Adjunctive ulotaront 50-75mg + usual antipsychotic  | No comparator group | SCZ | PANSS ≥ 70 | Open label PET study phase I,  | Change in dopamine synthesis capacity at week 2 using 18-F-DOPA  | 22 planned | 2 weeks  | In progress | UK | 2019 – 2021 (est.) | Due 2021  |
| NCT04325737 |  | Ulotaront (titrated from 50 to 100mg- cohort 1), ulotaront (titrated from 25 to 100mg- cohort 2) | Placebo | SCZ | Clinically stable  | Phase I | Frequency of SEs and SAEs | 32 planned | Cohort 1- 14 days Cohort 2- 17 days | In progress | Japan  | 2020- 2021 (est) | Due May 2021 |
| NCT04369391 |  | Ulotaront 150mg | Placebo,Moxifloxacin 400mg | SCZ | Clinically stable | Randomised, 3-period crossover study, phase I | Change from baseline QTc interval | 72 planned | 7 weeks  | In progress | USA | June – November 2020 (est.) | Due November 2020 |
| NCT02970929 | (Koblan, Kent et al. 2020) | Ulotaront 25mg, 50mg or 75mg  | No comparator group | SCZ | Acute relapse | Open labelled extension study, phase II | Primary outcome: incidence of AEs and SAEs Secondary outcome:Change from extension-study baseline in PANSS total score | 156 | 26 weeks | Completed | USA, Eastern Europe & Russia | 2016-2018 | N/A | Among patients who had initially been assigned to receive ulotaront and then continued treatment, the mean change from extension study baseline was -17.1.Among patients who had initially been assigned to receive placebo and then switched to open-label ulotaront in the extension study, the mean change from the extension study baseline was -27.9. |
| KiNCT02969382 | (Koblan, Kent et al. 2020) | Ulotaront 50 -75mg  | Placebo | SCZ | Acute relapse  | Double blinded RCT, phase II | Change in PANSS total score | 245  | 4 weeks | Completed | USA, Eastern Europe & Russia  | 2016-2018 | ↑ | Ulotaront vs placebo: mean difference -7.5, p<0.01 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaRCT: Randomised controlled trialAEs: Adverse eventsSAEs: Serious adverse eventsPANSS: Positive and negative symptom scale↑: Better outcome in ulotaront group relative to comparator group (statistically significant)↓: Poorer outcome in ulotaront group relative to comparator group (statistically significant)↔: No statistically significant difference between ulotaront and comparator groups |

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| **Table 11: Clinical efficacy trials of xanomeline in schizophrenia**  |
| **Identifier** | **Reference** | **Xanomeline dose(s)** | **Comparator group (s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location** | **Year** | **Results** |
| **Change in xanomeline group relative to comparator group** | **Effect size** |
|  | (Shekhar, Potter et al. 2008) | Xanomeline 25mg – 75mg TDS | Placebo TDS | SCZ or SZA  | Inpatients  | Pilot study, double-blind, placebo-controlled RCT | PANSS, BPRS, CGI | 20 | 4 weeks  | Completed | USA | 2008 | ↑ | PANSS: mean difference -24.0, p<0.05BPRS: mean difference -6.45, p<0.05CGI: mean difference +1.1, p=0.94List learning test: mean difference in score change +2.4, p<0.05Story recall test: mean difference +1.4, p<0.05 Delayed memory test: mean difference + 22.6, p<0.05No statistically significant difference between xanomeline and placebo groups for trail making test, continuous performance test, digit span, or domains of brief visuospatial memory test other than delayed memory.All mean differences relative to placebo. No multiplicity correction applied to cognition outcomes.  |
| NCT03697252 | (Brannan, Sawchak et al. 2021) | Xanomeline 50 – 125mg BD + trospium 20-30mg BD  | Placebo BD | SCZ | Acute relapse requiring hospitalisation | Double blinded RCT, phase II | PANSS total  | 182 | 5 weeks | Completed | USA | 2018 - 2019 | ↑ | PANSS: LSMD -11.6, p<0.001PANSS positive subscale: LSMD -3.2 (p<0.001)PANSS negative subscale: LSMD -2.3, p<0.001All mean differences relative to placebo. |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaSZA: Schizoaffective disorderPANSS: Positive and negative symptom scaleBPRS: Brief psychiatric rating scale CGI: Clinical Global ImpressionRCT: Randomised controlled trial LSMD: Least squares mean differenceBD: bis die: twice dailyTDS: ter die sumendus: three times a day↑: Better outcome in xanomeline group relative to comparator group (statistically significant)↓: Poorer outcome in xanomeline group relative to comparator group (statistically significant)↔: No statistically significant difference between xanomeline and comparator groups |

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| **Table 12: Clinical efficacy trials of BI 409306 in schizophrenia**  |
| **Identifier** | **Reference** | **BI 409306 dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in BI 409306 group relative to comparator group** | **Effect size** |
| NCT03351244 |  | BI 409306 ‘high dose’BI 409306 ‘low dose’ | Placebo | SCZ | Clinically stable  | Double blinded RCT, phase II | Time to first relapse | 264 planned | 28 weeks  | Terminated (disruption due to Covid-19) | North America, Europe, Asia | 2017-2021 | Study terminated |
| NCT03230097 |  | BI 409306 | Placebo | APS | Age 16-30 | Double blinded RCT, phase II | Time to remission from APS | 50 planned | 52 weeks  | Terminated (disruption due to Covid-19) | North America, Europe, Asia | 2017-2021 | Study terminated |
| NCT02281773 | (Brown, Nakagome et al. 2019) | Adjunctive BI 409306 10mg, 25mg, 50mg, 100mg | Adjunctive placebo | SCZ | Clinically stable  | Double blinded RCT, phase II | Change in MCCB score | 518 | 12 weeks | Completed | North America, Europe, Asia | 2014 - 2017 | ↔ | BI 409306 10mg vs placebo: mean difference -1.2, p=0.126BI 409306 25mg vs placebo: mean difference 0.3, p=0.733BI 409306 50mg vs placebo: mean difference 0.3, p=0.699BI 409306 100mg vs placebo: mean difference -0.6, p=0.42 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaAPS: Attenuated psychosis syndrome RCT: Randomised controlled trialMCCB: Matrics Consensus Cognitive BatteryMATRICS: Measurement and Treatment Research to Improve Cognition in SchizophreniaPANSS: Positive and Negative syndrome scale ↑: Better outcome in BI 409306 group relative to comparator group (statistically significant)↓: Poorer outcome in BI 409306 relative to comparator group (statistically significant)↔: No statistically significant difference between BI 409306 and comparator groups |

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| **Table 13: Clinical efficacy trials of BI 425809 in schizophrenia**  |
| **Identifier** | **Reference** | **BI 425809 dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in BI 425809group relative to comparator group** | **Effect size** |
| NCT04846868(CONNEX-1) |  | BI 425809 (dose not stated) | Placebo | SCZ | Clinically stable | Double blinded RCT, phase III, parallel group trial | Change in overall composite T-score of MATRICS CCB | 586 planned | 26 weeks | Recruiting | North America, South America, Asia & Europe | 2021 – 2024 (est.) | Results due 2024 |
| NCT04846881 (CONNEX-2) |  | BI 425809 (dose not stated) | Placebo | SCZ | Clinically stable | Double blinded RCT, phase III, parallel group trial  | Change in overall composite T-score of MATRICS CCB | 586 planned | 26 weeks  | Recruiting  | North America, South America, Asia & Europe(different sites to CONNEX-1) | 2021 – 2024 (est.) | Results due 2024 |
| NCT04860830 (CONNEX-3) |  | BI 425809 (dose not stated) | Placebo | SCZ | Clinically stable | Double blinded RCT, phase III, parallel group trial | Change in overall composite T-score of MATRICS CCB | 586 planned | 26 weeks | Recruiting  | North America, Asia & Europe | 2021 – 2024 (est.) | Results due 2024 |
| NCT03859973 |  | BI 425809 (dose not stated) + adjunctive computerised cognitive training  | Placebo + adjunctive computerised cognitive training | SCZ | Clinically stable | Double blinded RCT, phase II | Change in overall composite T-score of MATRICS CCB | 200 planned | 12 weeks | Recruiting  | North America, Europe & Australasia  | 2019-2022 | Results due 2022 |
| NCT02832037 | (Fleischhacker, Podhorna et al. 2021) | Adjunctive BI 425809 2mg, 5mg, 10mg, 25mg  | Adjunctive placebo | SCZ | Clinically stable  | Double blinded RCT, phase II | Change in MCCB score | 509 | 12 weeks  | Completed | North America, Europe & Asia | 2016-2021 | ↑ | BI 425809 10mg vs placebo: mean improvement 1.98, p<0.05BI 425809 25mg vs placebo: mean improvement 1.73, p<0.05 |
|  | **Key to abbreviations and symbols:**SCZ: SchizophreniaRCT: Randomised controlled trialAE: Adverse eventsMCCB: Measurement and Treatment Research to Improve Cognition Consensus Cognitive Battery↑: Better outcome in BI 425809 group relative to comparator group (statistically significant)↓: Poorer outcome in BI 425809 group relative to comparator group (statistically significant)↔: No statistically significant difference between BI 425809 and comparator groups |

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| **Table 14: Clinical efficacy trials of MK8189 in schizophrenia**  |
| **Identifier** | **Reference** | **MK8189 dose(s)** | **Comparator group(s)** | **Indication** | **Patient group** | **Type of study, phase** | **Primary outcome measure** | **Number of patients enrolled** | **Length of treatment**  | **Status**  | **Location**  | **Year** | **Results** |
| **Change in MK8189 group relative to comparator group** | **Effect size** |
| NCT04624243 |  | MK-8189 16mg, 24mg | Placebo | SCZ | Acute relapse | Double blinded RCT, phase II | Change in PANSS score | 576  | 12 weeks  | In progress | North America, Europe, Asia,  | 2020-2022 (est.) | Results due 2022 |
| NCT03055338 |  | MK-8189 12mg | Risperidone 6mg, placebo | SCZ | Acute relapse | Double blinded randomised controlled parallel group trial, phase II | Change in PANSS score | 224 | 4 weeks  | Completed | USA | 2017-2018 | ↔ | MK8189 vs placebo:Mean difference -4.7, p=0.074Risperidone vs placebo:mean difference -7.3, p=0.033 |
| **Key to abbreviations and symbols:**SCZ: SchizophreniaRCT: Randomised controlled trialPANSS: Positive and Negative Syndrome Scale AE: Adverse events↑: Better outcome in MK-8189 group relative to comparator group (statistically significant)↓: Poorer outcome in MK-8189 group relative to comparator group (statistically significant)↔: No statistically significant difference between MK-8189 and comparator groups |