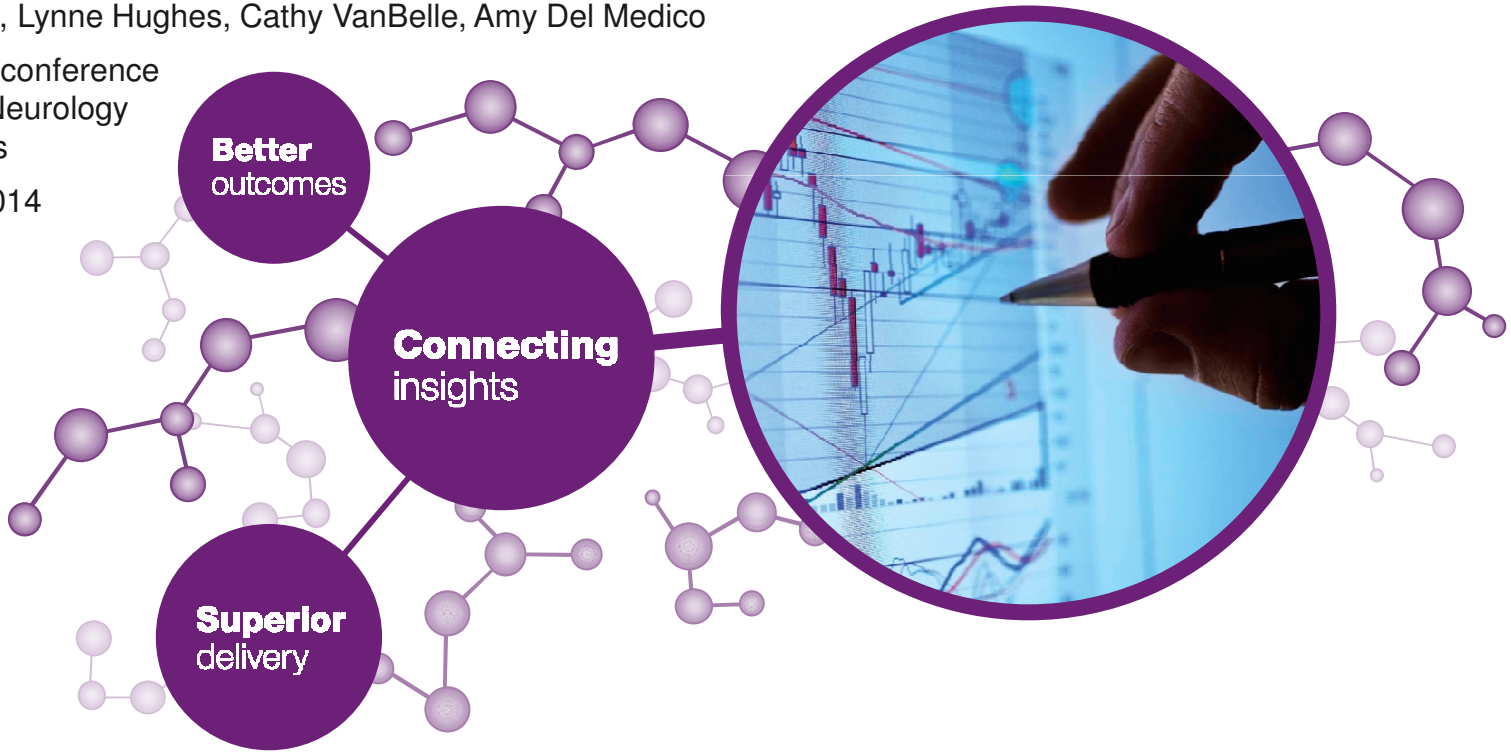
Novel therapeutic approaches in multiple sclerosis

Neuroprotective and remyelinating agents, the future of clinical trials in MS?

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3rd International conference
& Exhibition on Neurology
and Therapeutics

08 September 2014



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Multiple sclerosis

- Multiple sclerosis (MS) is the most frequent inflammatory disease of the central nervous system (CNS) and most common cause of neurological disability in young adults (> 2.5 M patients WW, mainly females)
- The inflammation results in Myelin destruction (demyelination) that will progressively lead to axonal injury and neuronal degeneration

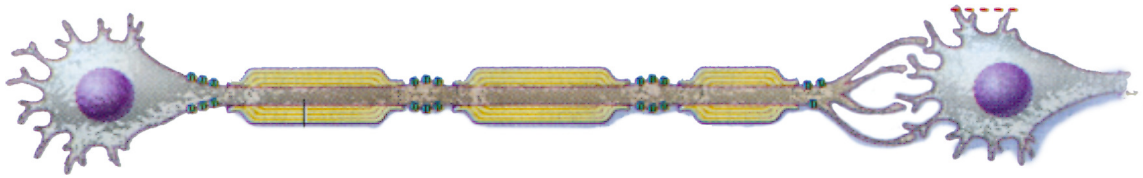


- **Characterized clinically by recurrent (Remitting relapsing forms) or chronically progressive neurological dysfunction (Progressive forms)**
- Leads to diverse clinical signs and symptoms of neurological dysfunction; unpredictable clinical course, variable prognosis
- Cause unknown but might be a result of combined, environmental, immunological and genetic susceptibility factors

Pathophysiology of MS

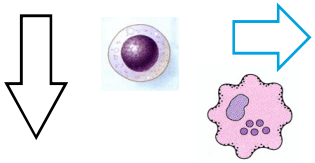
Demyelination and axonal loss

A Normal Neuron



Information flows

Demyelination



Remyelination

Relapse

A demyelinated neuron



Partial information flow

Disability

A degenerated neuron

Neurological symptoms



No information flow

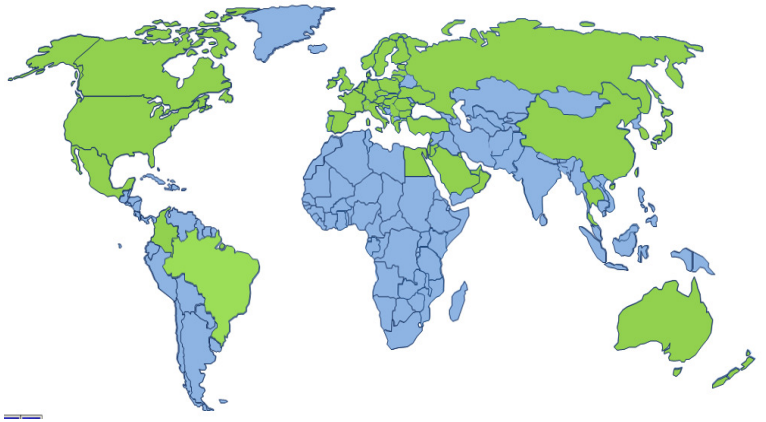
Therapies

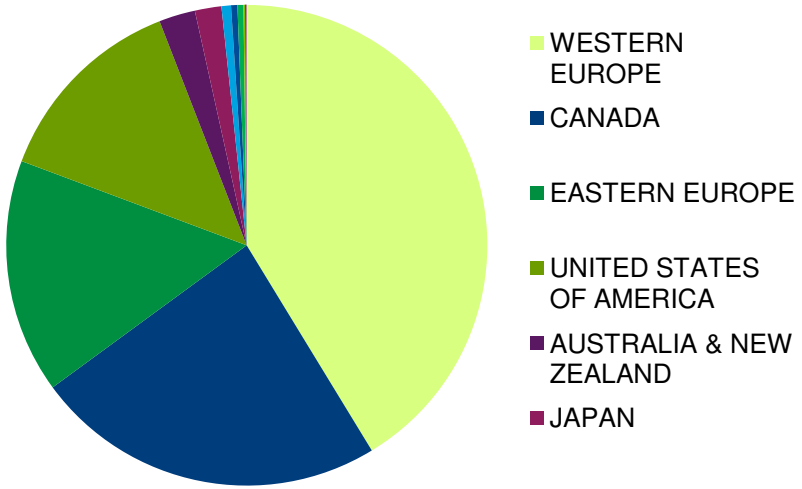
- Treatments modifying the outcome of acute relapses
- Therapies aimed at modifying the course of the disease: immunomodulators e.g. interferons, glatiramer, natalizumab and immunosuppressants ex. Mitoxantrone
- Symptomatic therapies
- Largely injectables, three oral therapies approved since 2010
- Future therapies focusing on neuroprotection or restoration of neurological function (ex. Promoters of remyelinisation)

Quintiles Multiple Sclerosis experience

2000-2013

- **43** studies enrolled
- **19,000**+ MS patients recruited
- **1100**+ recruiting sites
- Pool of **3,500**+ sites in **65** countries
- **230** CNS Project Managers
- **25** Medical Specialists in CNS





Our experience includes:

DMT's: Beta interferon Immunomodulators

Biosimilars

Gene therapy

V-CAMs

B cell depleting therapies

Anti-Cancer Agents

S1P Receptor Modulator

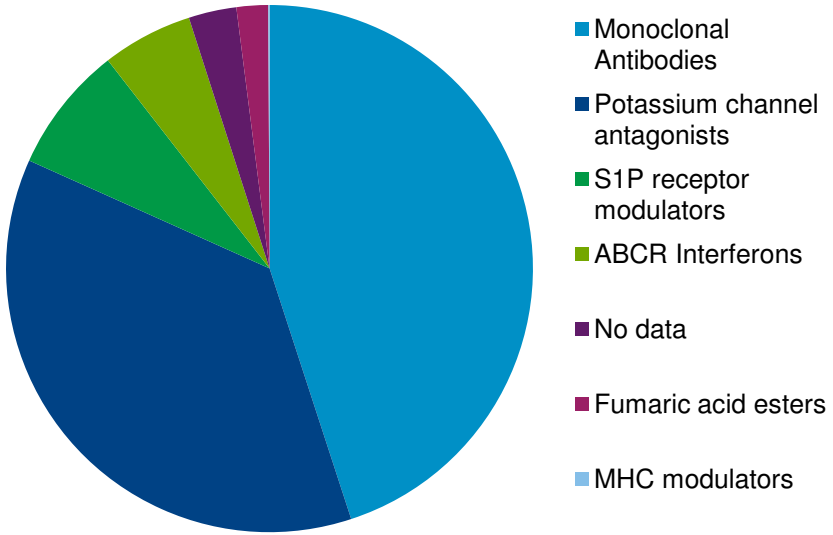
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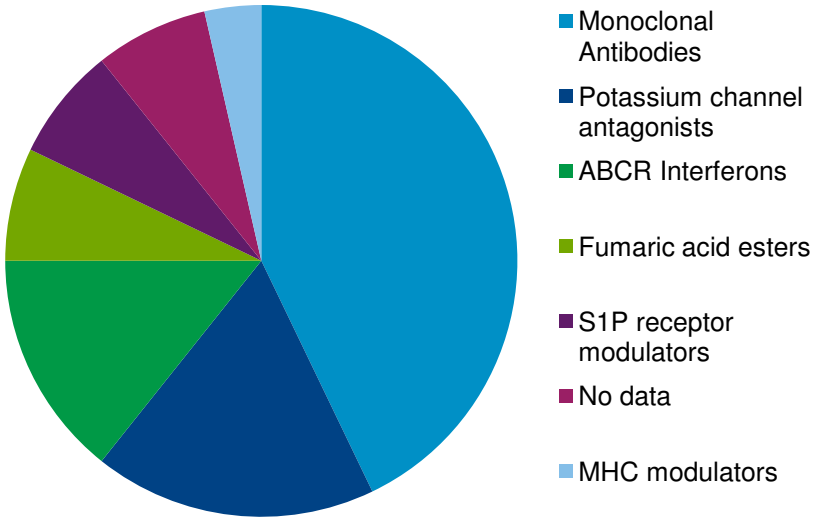
Source: Quintiles Proprietary Data 11Jul2014

Quintiles' contribution per MoA

With three decades of experience and unmatchable therapeutic expertise Quintiles is the number one CRO in MS – we have worked on 16 of the MS compounds developed since 2000



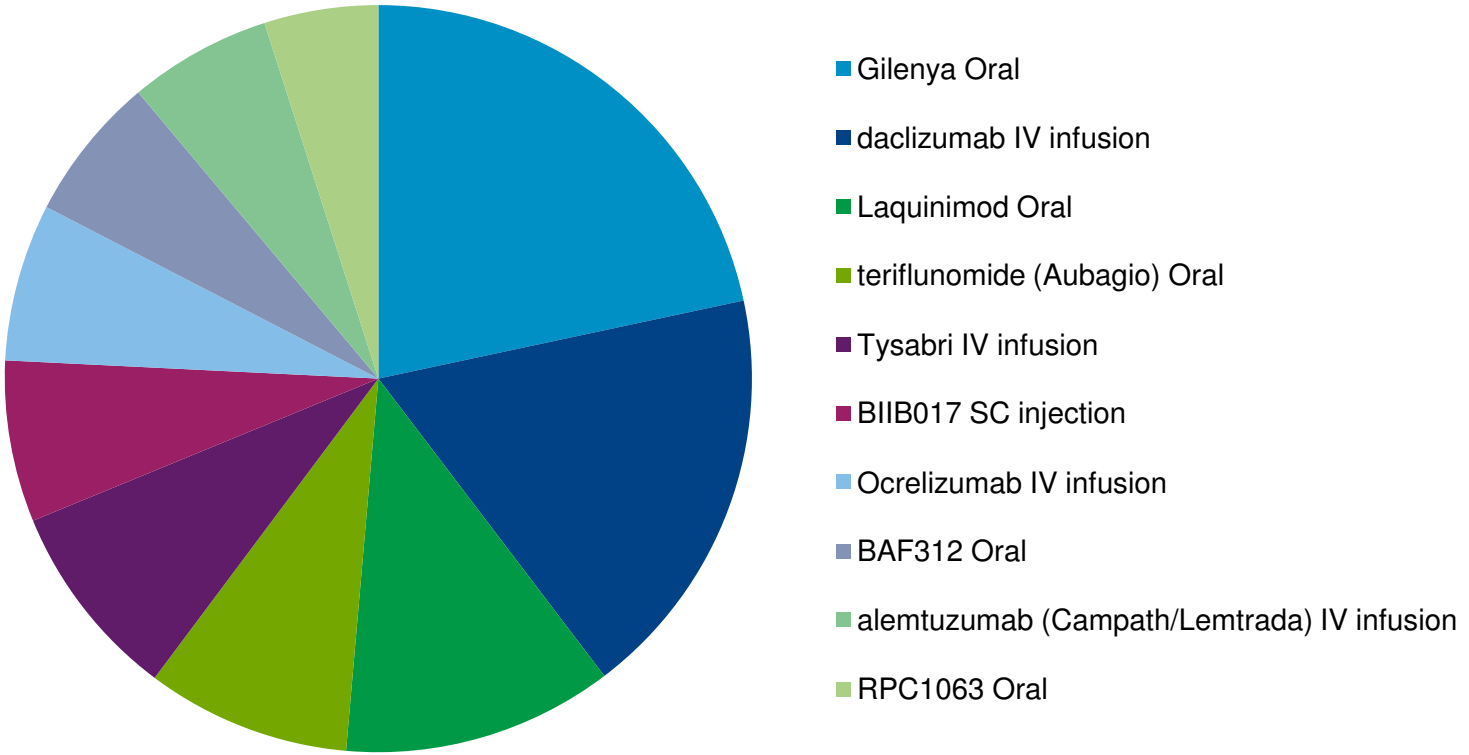
Source: Quintiles Proprietary Data 11Jul2014



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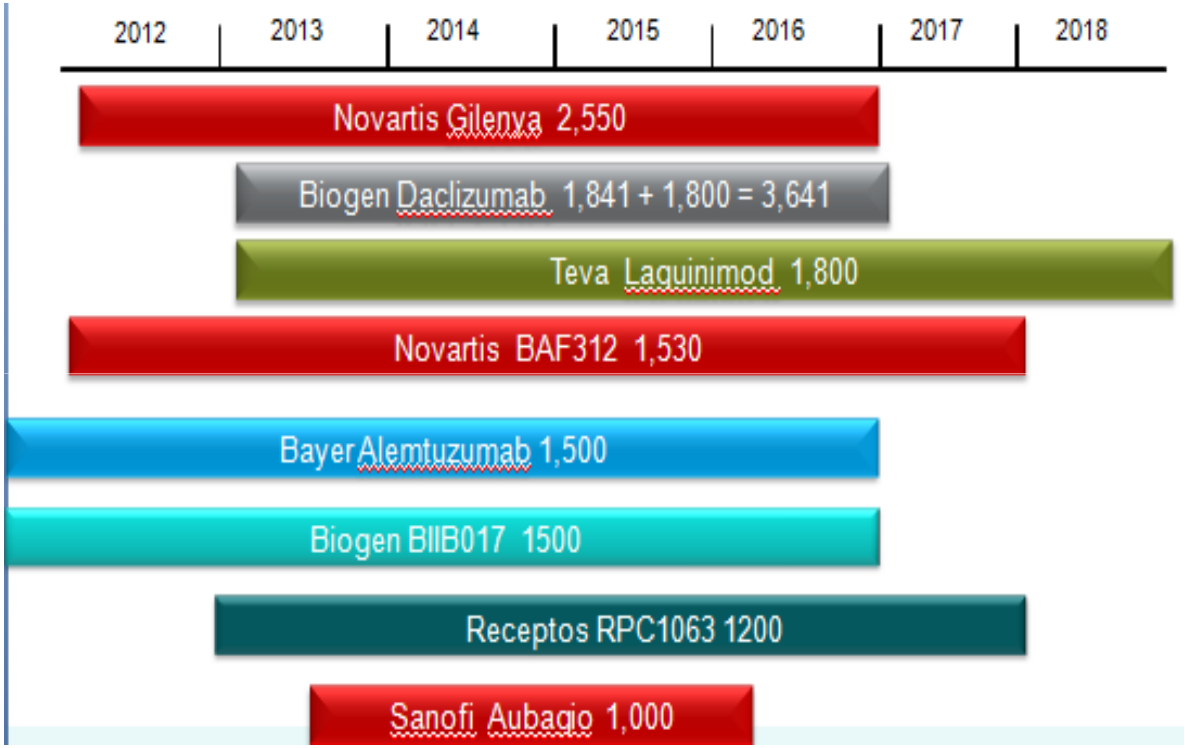
Quintiles has developed an internal, proprietary database using illustrative, de-identified data from many sources.

Top 10 most studied compounds

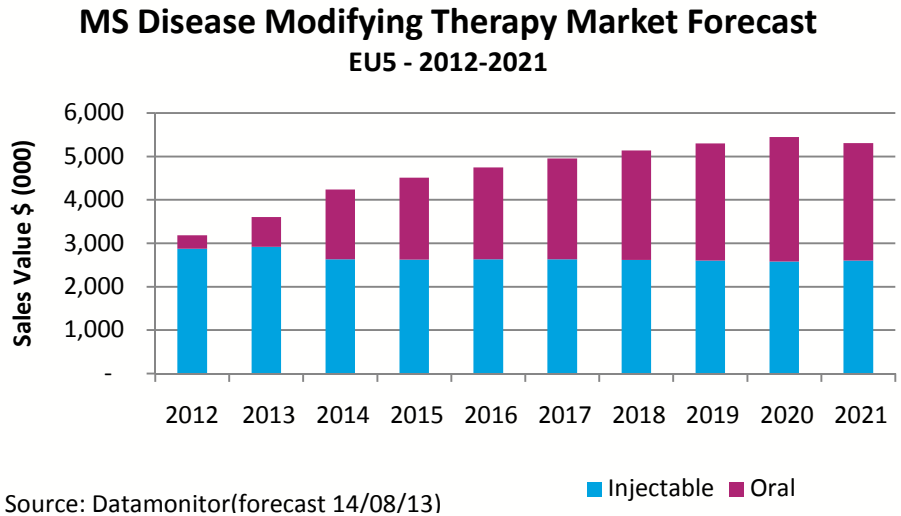


Industry sponsored, interventional studies by patient contribution

Current competitive landscape in the area of RRMS



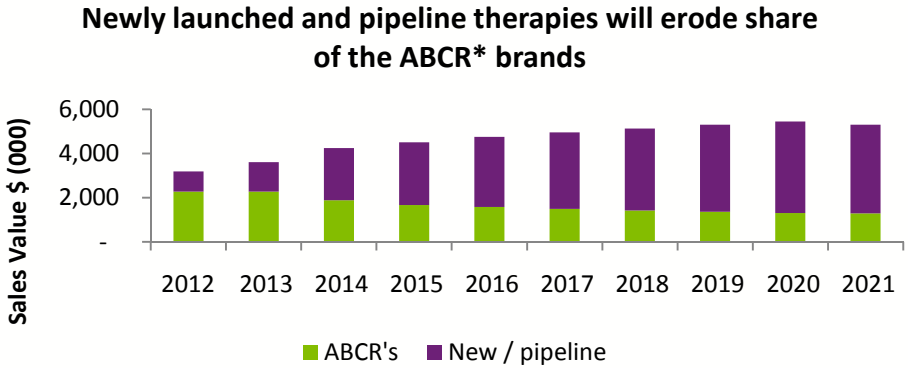
The MS market is forecast to peak in 2020, driven by the continuing uptake of novel oral therapies



Source: Datamonitor(forecast 14/08/13)

- The MS market in EU5# is expected to grow by $2.2b by 2020
- Generic and biosimilar entrants post 2020 will start to erode the market
- Injectable treatments will retain 50% share of the MS market

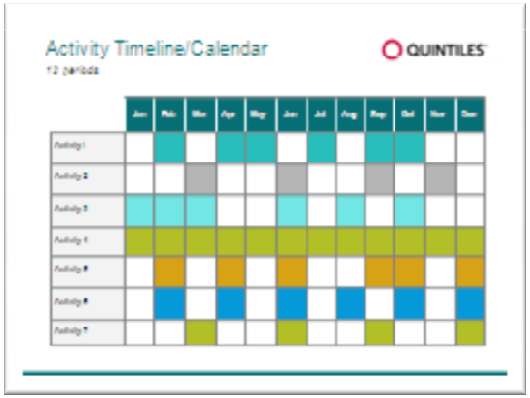
- In addition to continued growth from Gilenya. Tecfidera, Aubagio and Plegridy are expected to make the greatest market share gains.



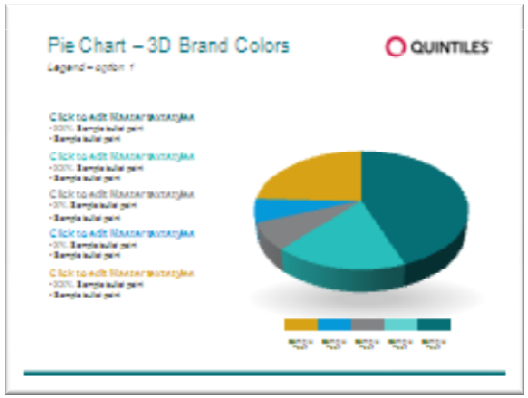
*Source: Datamonitor Forecast 14/08/13 *ABCR Brands = Avonex†, Betaseron†, Copaxone¥, Rebif†*
(† ß-interferon & ¥ glatiramer acetate therapies) # EU 5 (France, Germany, Italy, Spain, UK)

Background

With the ever-growing competitive landscape in conducting Multiple Sclerosis (MS) clinical trials and the unmet needs for more robust effects on long term disability and disease progression, novel therapies targeting different MS clinical forms and acting beyond relapse outcomes, are needed.

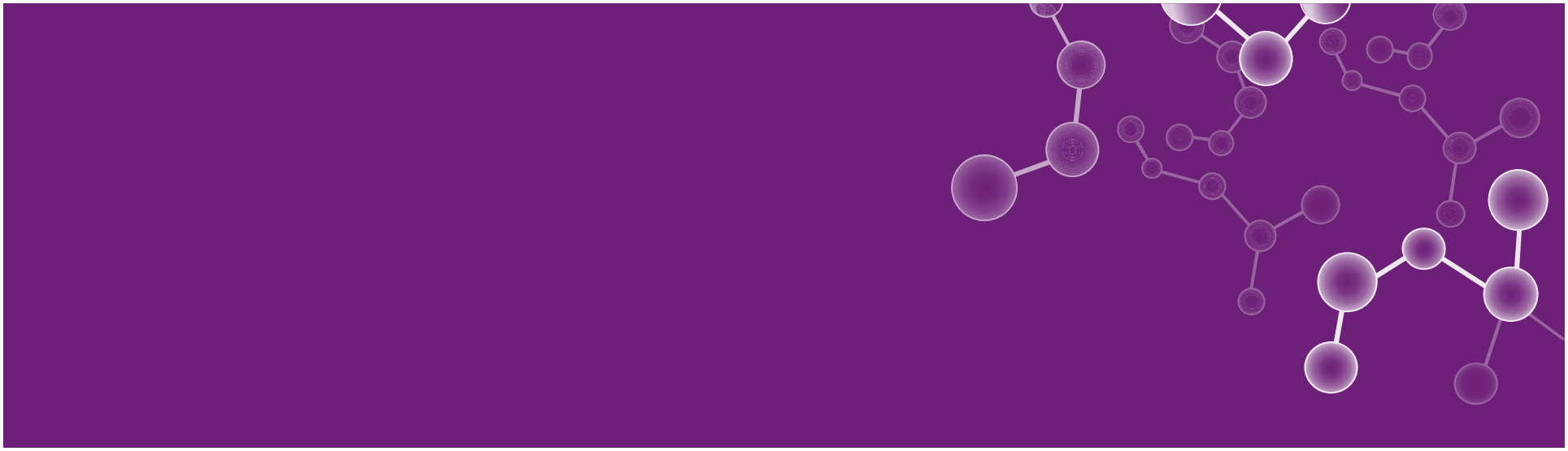






Objectives

- By 2020, more than 19 compounds would have been put on the market essentially, modifying the outcome of acute relapses in Relapsing Remitting forms of MS (RRMS)
- No approved therapies for progressive forms
- Clinical trials in primary and secondary progressive MS forms (PPMS and SPMS) remain more confidential
- The underlying mechanisms leading to neuronal loss and degeneration as a consequence of the initial demyelinating process are becoming more understood
- Agents providing neuroprotection or promoting remyelination are a growing necessity and need to be the focus of future clinical trials



Methods

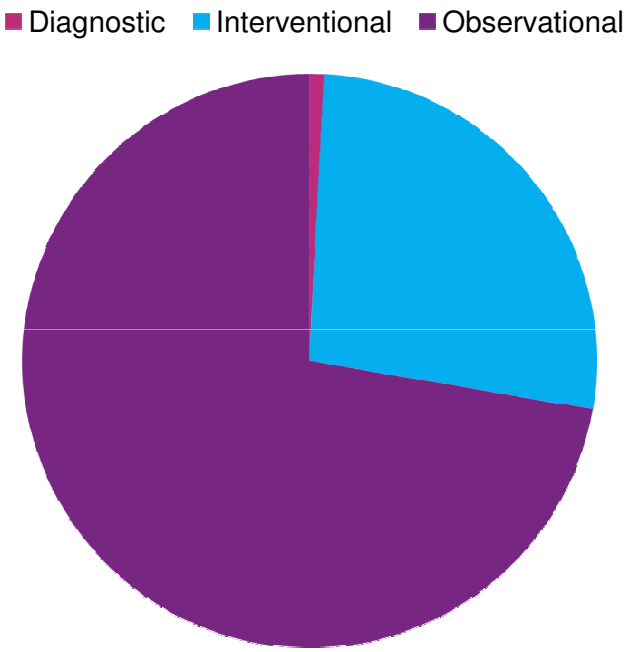
Retrospective analysis of Quintiles MS performance on 40 trials, as well as a review of more than 350 global clinical MS studies, available in the public domain (clinicaltrials.gov), has shown that the main focus of clinical research remains RRMS

Results

- Over 37,000 RRMS patients are currently participating in global interventional clinical trials where ARR remains the primary objective (> 70,000 RRMS patients in total, if observational studies added)
- Approximately 7,000 patients with progressive forms of MS are taking part in clinical research where effect on disability is studied as a primary outcome.
- When it comes to patients with CIS (Clinically Isolated Syndrome) and NMO (Neuromyelitis Optica), this number drops below 1500.
- The search on drugs in development reveals 25 investigational injectable compounds from phase 1 to phase 3b and another 15 investigational oral compounds, both currently developed, primarily, in RRMS.
- Only very few neuroprotective and remyelination therapeutic trials for MS are ongoing, six and four respectively.
- Furthermore, there are 16 stem cell trials being investigated as potential remyelinating agents.

Active MS studies

Total patients targeted by study type and MS sub-indication

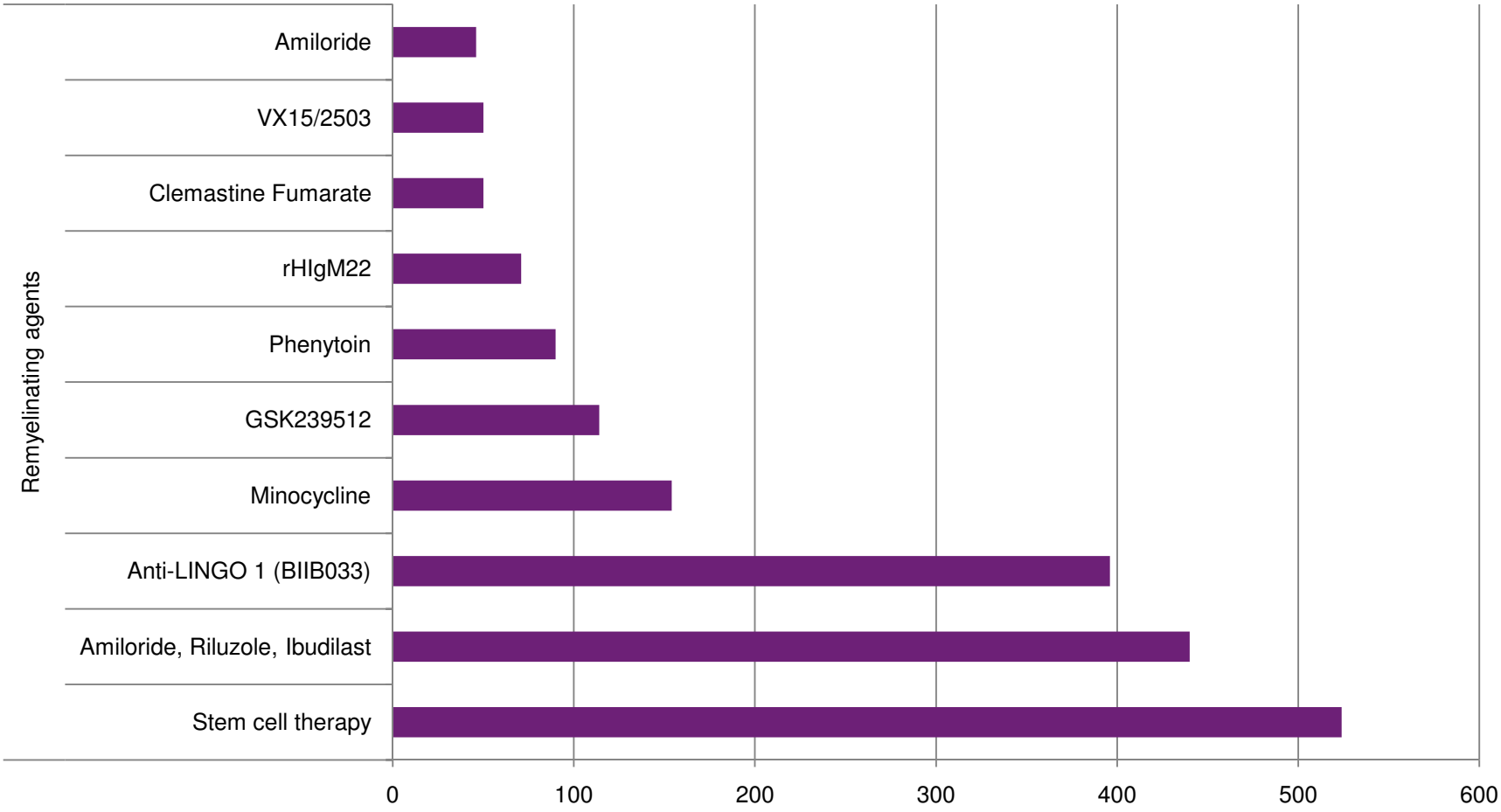


Sub-Indication	Diagnostic	Interventional	Observational
All MS	914	8,436	79,484
CIS	375	796	120
NMO		284	30
Pediatric MS		202	1,970
Progressive MS	100	7,048	700
RRMS		28,754	41,138
Grand Total	**1,389**	**45,520**	**123,442**

Over 170,000 MS patients will be recruited into 339 interventional, observational and diagnostic studies

Patient contribution to remyelinating/neuroprotective agents studies

(Source: clinicaltrials.gov 02Jul2014)



Conclusion

- The current MS clinical trials environment focuses mainly on developing drugs targeting the reduction of the ARR in RRMS patients in a consistently increasing competitive arena.
- Thus, it is becoming more and more challenging finding patients willing to participate in clinical research with so many therapies available to them and additional products scheduled to arrive on the global market in the near future.
- Our analysis reveals that it is essential that more effort is deployed in developing agents in more progressive forms of MS and those that have more significant effect on disability outcomes.
- Although clinical trials with compounds developed as remyelinating agents remain limited for different scientific and methodological reasons, it is crucial that this area expands to meet an unmet need: robust and positive effect on long term disability and disease progression in MS patients.